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71 Applicant: **Research Corporation, 405 Lexington Avenue, New York, N.Y. 10174 (US)**

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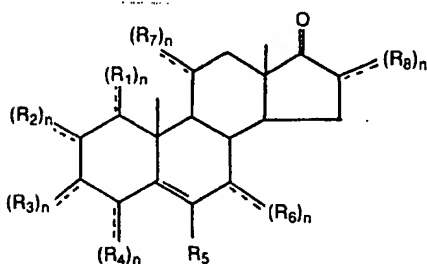
72 Inventor: **Schwartz, Arthur G., 220 Locust Street, Philadelphia Pennsylvania (US)**
Inventor: **Williams, John R., 824 North Woodbine Avenue, Penn Valley Pennsylvania (US)**

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74 Representative: **Brauns, Hans-Adolf, Dr. rer. nat. et al, Hoffmann, Eitle & Partner, Patentanwälte Arabellastrasse 4, D-8000 Munich 81 (DE)**

54 Steroids and therapeutic compositions containing same.

57 Steroids of the formula



and a therapeutic composition containing same which are useful as anti-cancer, anti-obesity, anti-hyperglycemic, anti-auto-immune and anti-hypercholesterolemic agents.

Although, DHEA-sulfate is the main precursor of placental estrogen and may be converted into active androgens in peripheral tissue, there is no obvious biological role for either DHEA or DHEA-sulfate in the normal individual. Several retrospective and prospective studies suggest that women with sub-normal levels of these steroids may be predisposed to develop breast cancer. For example, see Brownsey et al., "Plasma dehydroepiandrosterone sulfate levels in patients with benign and malignant breast disease," Eur. J. Cancer, 8, 131-137 (1972); Bulbrook et al., "Relation between urinary androgen and corticoid excretion and subsequent breast cancer," Lancet, 2, 395-398 (1971); Rose et al. "Plasma dehydroepiandrosterone sulfate, androstenedione and cortisol, and urinary free cortisol excretion in breast cancer," Eur. J. Cancer, 13, 43-47 (1977); Wang et al., "Studies on the sulfate esters of dehydroepiandrosterone and androsterone in the blood

1 of women with breast cancer," Eur. J. Cancer, 10, 477-482
(1974); and Zumoff et al., "Abnormal 24-hr mean plasma
concentrations of dehydroisoandrosterone and dehydroiso-
androsterone sulfate in women with primary operable breast
5 Cancer," Cancer Research, 41, 3360-3363, September 1981.

It has also been established that DHEA is a
potent non-competitive inhibitor of mammalian glucose-
6-phosphate dehydrogenase (G6PDH). For example, see
Oertel et al. "The effects of steroids on glucose-6-
10 phosphate dehydrogenase," J. Steroid Biochem., 3, 493-496
(1972) and Marks et al. "Inhibition of mammalian glucose-
6-phosphate dehydrogenase by steroids," Proc. Nat'l. Acad.
Sci, USA, 46, 447-452 (1960). Moreover, Yen et al. "Pre-
vention of obesity in A^{VY}/a mice by dehydroepiandro-
15 sterone," Lipids, 12, 409-413 (1977), reported that long-
term administration of DHEA to VY-A^{VY}/a mice prevented
the development of obesity without suppressing appetite.

Furthermore, it is also known that the long-
term treatment of C3H mice with DHEA, in addition to
20 reducing weight gain without suppressing appetite,
markedly inhibits spontaneous breast cancer development
and may delay the rate of aging. It has been observed that
DHEA antagonizes the capacity of the tumor promoter,
12-0-tetradecanoylphorbol-13-acetate, to stimulate
25 ³H-thymidine incorporation in mouse epidermis and in
a cultured rat kidney epithelial cell line. See,
Schwartz, "Inhibition of spontaneous breast cancer
formation in female C3H-A^{VY}/a mice by long-term treatment
with dehydroepiandrosterone," Cancer Res., 39, 1129-1132

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1 (1979); and Schwartz et al., "Dehydroepiandrosterone:
an anti-obesity and anti-carcinogenic agent," Nut.
Cancer 3, 46-53 (1981).

Ben-David et al., "Anti-hypercholesterolemic
5 effect of dehydroepiandrosterone in rats," Proc. Soc.
Expt. Biol. Med., 125, 1136-1140 (1967) have observed
that DHEA treatment has an anti-hypercholesterolemic
effect in mice, while Coleman et al. (Diabetes 31, 830,
1982) report that administration of DHEA produces a
10 marked hypoglycemic effect in C57BL/KsJ-db/db mice. The
latter authors suggest that the therapeutic effect of
DHEA might result from its metabolism to estrogens.

It is further known that DHEA and 16 α -bromo-
epiandrosterone are inhibitors of Epstein-Barr virus-
15 induced transformation of human lymphocytes and that
16 α -bromo-epiandrosterone is a more potent inhibitor
of mammalian G6PDH than DHEA. See, Schwartz et al.
Carcinogenesis, Vol. 2 No. 7, 683-686 (1981).

While DHEA has been found effective in the
20 afore-described manners, there is, however, evidence of an
estrogenic effect after prolonged administration. DHEA
is not an estrogen per se but is well known to be con-
vertible into estrogens. In addition, the therapeutic
dose of DHEA is rather high. It would therefore be
25 highly desirable to provide steroids, which while having
the same afore-described advantages of DHEA are more potent
and do not produce an estrogenic effect.

Accordingly, the present invention provides
novel steroids.

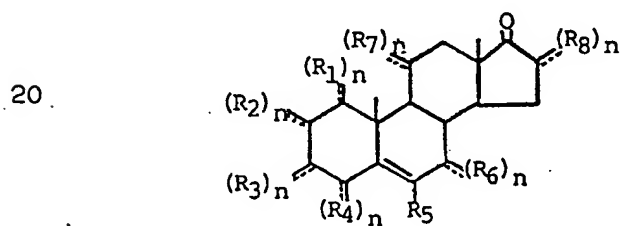
1 The steroids of the present invention exhibit significant and desirable pharmacological properties, and are particularly useful as cancer preventive agents.

5 These steroids are additionally useful as anti-obesity agents, anti-hyperglycemic agents, anti-aging agents, and anti-hypercholesterolemic agents.

 This invention further provides steroids
10 useful as anti-cancer, anti-obesity, anti-hyperglycemic, anti-aging and anti-hypercholesterolemic agents, which do not evidence estrogenic effects.

 The present invention also provides a process for the treatment and/or prevention of cancer,
15 obesity, aging, diabetes, and hyperlipidemia.

 The present invention provides novel steroids of the general formula:



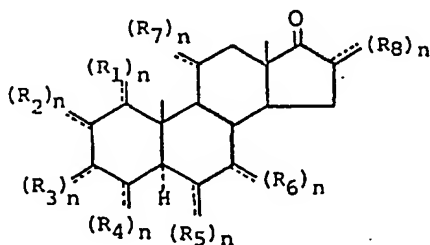
 wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are each inde-
25 pendentlly selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen and hydroxyl, n is an integer from 1 to 2 inclusive with the proviso that when R₁, R₂, R₃, R₄, R₆, R₇ or R₈ are alkenyl or
30 alkynyl, n is 1; with the further provisos that when

1 R_3 is hydroxy, any one of the substituents $R_1, R_2, R_4, R_5, R_6, R_7$ or R_8 is other than hydrogen; when R_3 is hydroxy, R_1 may only be alkyl when any one of R_2, R_4, R_5, R_6, R_7 or R_8 is other than hydrogen; when R_3 is hydroxy, R_2 may only be hydroxy when any one of R_1, R_4, R_5, R_6, R_7 or R_8 is other than hydrogen; when R_3 is hydroxy, R_4 may only be halogen with R_1, R_2, R_5, R_6, R_7 or R_8 is other than hydrogen; when R_3 is hydroxy, R_6 may only be hydroxy or methyl when R_1, R_2, R_4, R_5, R_7 or R_8 is other than hydrogen; when R_3 is hydroxy, R_7 may only be hydroxy when R_1, R_2, R_4, R_5, R_6 or R_8 is other than hydrogen; and when R_3 is hydroxy, R_8 may only be methyl, ethyl, hydroxy or halogen when R_1, R_2, R_4, R_5, R_6 or R_7 is other than hydrogen; and

15 when R_3 is hydroxy, R_5 may be alkyl only when R_1, R_2, R_4, R_6, R_7 or R_8 are other than hydrogen. Preferably, R_3 is alkyl of from 1 to 10 carbon atoms and most preferably lower alkyl of from 1 to 5 carbon atoms.

The present invention further provides

20 novel steroids of the formula:

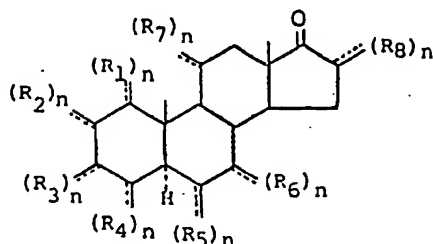


1 wherein R_1 - R_8 are selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, halogen and hydroxyl,
n is an integer from 1 to 2 inclusive with the proviso
that when R_1 - R_8 are alkenyl or alkynyl n is 1 and with
5 the further provisos that R_3 may be hydroxy or halogen
only when any one of R_1 , R_2 , R_4 , R_5 , R_6 , R_7 or R_8 is
other than hydrogen; when R_3 is hydroxy, R_1 may be
hydroxy or halogen only when any one of R_2 , R_4 , R_5 , R_6 ,
 R_7 or R_8 is other than hydrogen; when R_3 is hydroxy,
10 R_2 may be methyl or halogen only when any one of R_4 ,
 R_5 , R_6 , R_7 or R_8 is other than hydrogen; when R_3 is
hydroxy, R_4 may be halogen, methyl or hydroxy only
when any one of R_1 , R_2 , R_3 , R_5 , R_6 , R_7 or R_8 is other
than hydrogen; when R_3 is hydroxy, R_5 may be methyl,
15 halogen or hydroxy only when R_1 , R_2 , R_4 , R_6 , R_7 or R_8
is other than hydrogen; when R_3 is hydroxy, R_6 may be
hydroxy or methyl only when R_1 , R_2 , R_4 , R_5 , R_7 or R_8
is other than hydrogen; when R_3 is hydroxy, R_7 may be
hydroxy only when R_1 , R_2 , R_4 , R_5 , R_6 or R_8 is other
20 than hydrogen; and when R_3 is hydroxy, R_8 may be methyl,
hydroxy or halogen only when R_1 , R_2 , R_4 , R_5 , R_6 or R_7
is other than hydrogen.

The present invention additionally provides
processes for the prophylaxis of cancer, obesity, aging,
25 diabetes and hyperlipidemia by administering to a host,
e.g. mammals, a therapeutically effective amount of the
afore-identified steroids.

The present invention further provides pro-
cesses for the prophylaxis of cancer, obesity, aging,
30 diabetes, hyperlipidemia comprising administering to

1 a host, e.g. mammals, a therapeutically effective amount of
the afore-identified steroids or a steroid having the general
formula:



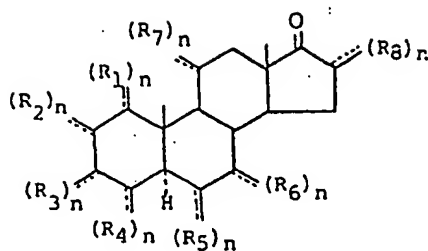
wherein R_1 - R_8 are selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, halogen and hydroxyl,
15 n is an integer from 1 to 2 inclusive and with the pro-
viso that when R_1 - R_8 are alkenyl or alkynyl n is 1.

In accordance with the present invention, it
has been surprisingly discovered that steroids having a
certain structure, described hereinafter in more detail,
20 are characterized with significant pharmacological pro-
perties without toxic or undesirable estrogenic effects.
That is, it has been quite unexpectedly discovered that
the steroids of the present invention are useful as can-
cer preventive, anti-obesity, anti-diabetic, anti-aging
25 and anti-hypercholesterolemic agents, but unlike DHEA are
more potent and exhibit very little or no estrogenic
effects.

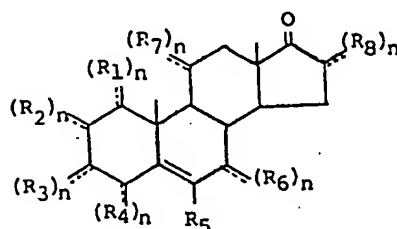
More particularly, the steroids of the present
invention have the general formulas:

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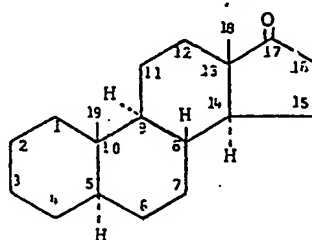
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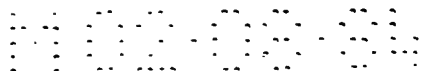


and



15 wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are as defined hereinbefore. The R_1 - R_8 substituents are designated as being in the α -position by means of a broken line (---) joining the substituent to the steroid nucleus, the substituents are designated as being in the β -position by means of a solid line (—) joining the substituent to the steroid nucleus and in those cases in which the substituent may be either in the α - or β - position the substituents are indicated as being joined to the steroid nucleus by a broken line and a solid line placed side to side. Furthermore, in accordance with I.U.P.A.C. nomenclature, the carbon atoms of the steroids of the present invention are numbered as follows and the steroids have the designated I.U.P.A.C. stereochemistry:





1 Specific illustrative compounds within the
above structural formulas and useful in accordance with
the present invention include:

- 3 β -hydroxy-1 α -methylandrost-5-en-17-one.
1 α -methylandrost-5-en-17-one
5 1 α -methyl-5 α -androstan-17-one
3 β -hydroxy-2 α -methylandrost-5-en-17-one
2 α -ethynyl-3 β -hydroxyandrost-5-en-17-one
3 β -hydroxy-2 α ,6-dimethylandrost-5-en-17-one
10 2 α ,6,16 α -trimethylandrost-5-en-17-one
3 β -hydroxy-2 α ,6,16 α -trimethylandrost-5-en-17-one
3 β -hydroxy-2 α -ethynyl-6,16 α -dimethylandrost-5-en-17-one
2 α -ethynyl-6-chloroandrost-5-en-17-one
3 β -methylandrost-5-en-17-one
15 3 β -ethenylandrost-5-en-17-one
3 β -ethynylandrost-5-en-17-one
3 β -ethynyl-6-methylandrost-5-en-17-one
3 β -ethynyl-6-chloroandrost-5-en-17-one
3 β -ethynyl-6-chloro-16 α -methylandrost-5-en-17-one
20 3 β -ethylandrost-5-en-17-one
3 β -butylandrost-5-en-17-one
3 β -ethynyl-6,16 α -dimethylandrost-5-en-17-one
3 β ,16 α -diethynylandrost-5-en-17-one
3 β -ethynyl-6-methyl-16 α -ethylandrost-5-en-17-one
25 3 β -ethynyl-7 β -methylandrost-5-en-17-one
2 α ,7 β -dimethylandrost-5-en-17-one
1 α -chloro-3 β -methylandrost-5-en-17-one
3 β -hydroxy-4 α -methylandrost-5-en-17-one
3 β -hydroxy-4 α -ethynylandrost-5-en-17-one
30 3 β -hydroxy-4 α -ethenylandrost-5-en-17-one
3 β -hydroxy-16 α -ethyl-4 α -ethynylandrost-5-en-17-one

- 1 3 β -hydroxy-16 α -methyl-4 α -ethynylandrost-5-en-17-one
2 α ,3 β -dihydroxyandrost-5-en-17-one
2 α ,3 β -diethynylandrost-5-en-17-one
3 β -hydroxy-4,6-dimethylandrost-5-en-17-one
- 5 3 β -methyl-4 α -ethynylandrost-5-en-17-one
3 β -methyl-7 β -chloroandrost-5-en-17-one
3 β -methyl-16 α -ethylandrost-5-en-17-one
3 β -methyl-16 α -ethynylandrost-5-en-17-one
3 β -hydroxy-6-ethylandrost-5-en-17-one
- 10 3 β -hydroxy-11 α -methylandrost-5-en-17-one
3 β -hydroxy-11 α -chloroandrost-5-en-17-one
3 β -hydroxy-16 α -methylandrost-5-en-17-one
3 β -hydroxy-16 α -ethylandrost-5-en-17-one
3 β -hydroxy-16 α -ethenylandrost-5-en-17-one
- 15 3 β -hydroxy-16 α -ethynylandrost-5-en-17-one
3 β -hydroxy-6-ethenylandrost-5-en-17-one
3 β -hydroxy-6-ethynylandrost-5-en-17-one
2 α -methyl-3 β -hydroxy-6-ethynylandrost-5-en-17-one
3 β -hydroxy-7 β -methylandrost-5-en-17-one
- 20 3 β -hydroxy-7 β -ethenylandrost-5-en-17-one
3 β -hydroxy-7 β -ethynylandrost-5-en-17-one
2 α -methyl-3 β -hydroxy-7 β -ethynylandrost-5-en-17-one
2 α ,3 β -dimethylandrost-5-en-17-one
3 β ,4 α -dimethylandrost-5-en-17-one
- 25 2 α ,3 β -diethynylandrost-5-en-17-one
3 β ,4 α -diethynylandrost-5-en-17-one
2 α ,3 β -diethenylandrost-5-en-17-one
3 β ,4 α -diethenylandrost-5-en-17-one
2 α ,3 β ,6-trimethylandrost-5-en-17-one
- 30 3 β ,4 α ,7 β b-trimethylandrost-5-en-17-one

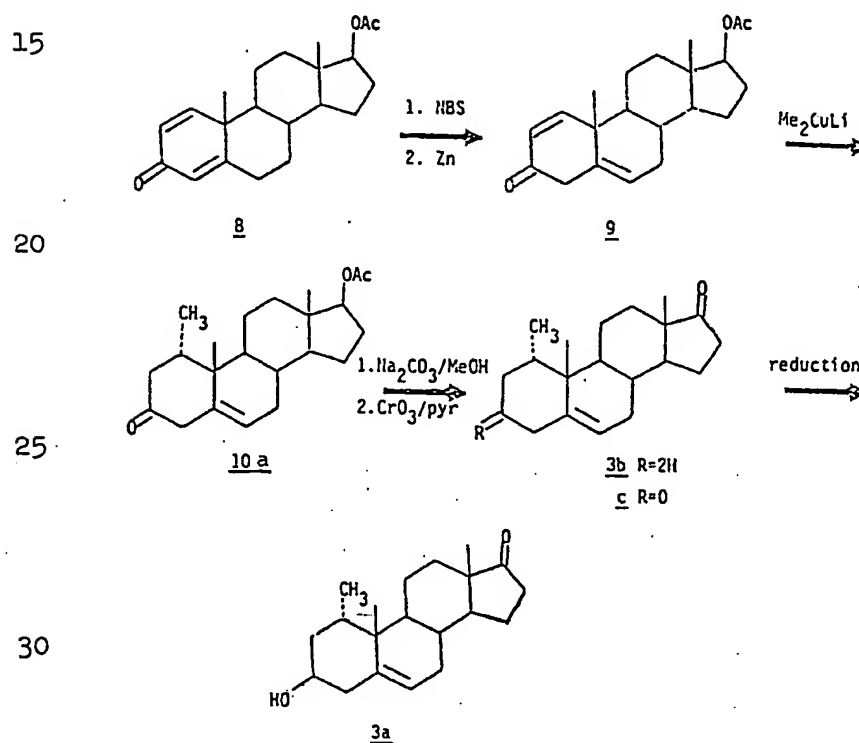
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- 1 3 β -ethynyl-7 β -methylandrost-5-en-17-one
6-methylandrost-5-en-17-one
7 β -methylandrost-5-en-17-one
11 α -methylandrost-5-en-17-one
- 5 16 α -methylandrost-5-en-17-one
3 β -hydroxy-4,4-difluoroandrost-5-en-17-one
3 β -hydroxy-16,16-difluoroandrost-5-en-17-one
2 α -fluoro-3 β -hydroxyandrost-5-en-17-one
3 β -hydroxy-6-bromoandrost-5-en-17-one
- 10 3 β -methyl-5 α -androstan-17-one
3 β -methyl-4 α -ethynyl-5 α -androstan-17-one
3 β -methyl-7 β -chloro-5 α -androstan-17-one
3 β -methyl-16 α -ethyl-5 α -androstan-17-one
3 β -methyl-16 α -ethynyl-5 α -androstan-17-one
- 15 3 β -hydroxy-6-ethyl-5 α -androstan-17-one
3 β -hydroxy-11 α -methyl-5 α -androstan-17-one
3 β -hydroxy-11 α -chloro-5 α -androstan-17-one
3 β -hydroxy-16 α -methyl-5 α -androstant-17-one
3 β -hydroxy-16 α -ethyl-5 α -androstant-17-one
- 20 3 β -hydroxy-16 α -ethynyl-5 α -androstan-17-one
3 β -hydroxy-6-ethenyl-5 α -androstan-17-one
2 α -methyl-3 β -hydroxy-6-ethynyl-5 α -androstan-17-one
3 β -hydroxy-7 β -methyl-5 α -androstan-17-one
3 β -hydroxy-7 β -ethenyl-5 α -androstan-17-one
- 25 3 β -hydroxy-7 β -ethynyl-5 α -androstan-17-one
2 α -methyl-3 β -hydroxy-7 β -ethynyl-5 α -androstan-17-one
2 α ,3 β -dimethyl-5 α -androstan-17-one
3 β ,4 α -dimethyl-5 α -androstan-17-one
2 α ,3 β -diethynyl-5 α -androstan-17-one
- 30 3 β ,4 α -diethynyl-5 α -androstan-17-one
2 α ,3 β -diethenyl-5 α -androstan-17-one
16 α -bromo-3 β -methylandrost-5-en-17-one
- 35

1 The steroids of the present invention may be prepared in accordance with conventional organic syntheses or if known may be commercially obtained. The following procedures are illustrative of some procedures
5 which may be utilized to prepare the steroids included herein:

A representative procedure for alkylation at carbon-1 and specifically the synthesis of a 1 α -methyl DHEA 3a and 1 α -methyl-desoxy DHEA 3b is given in
10 Scheme 1.

Scheme 1



- 1 Allylic bromination (e.g. with N-bromosuccinimide (NBS)) of 17 β -acetoxyandrosta-1,4-dien-3-one 8 followed by treatment with zinc affords the non-conjugated enone 9.
1,4-Alkylation with lithiodimethyl cuprate provides the
5 1 α -methyl ketone 10a. At this stage the 10a may be converted to a methylene by Wolff-Kishner reduction. These vigorous reaction conditions result in hydrolysis of the resulting carbon-17 acetate thereby yielding the hydroxy desoxy derivative, 17 β -hydroxy-1 α -methylandrost-5-ene (3b)
10 Both 10a and its desoxy derivative can be converted via standard reactions i.e. hydrolysis of the 17-acetate with sodium carbonate and methanol followed by chromium trioxide oxidation of the resulting 17-alcohol to the carbon-17 ketone. Selective reduction of the carbon-3 ketone, 3,17-
15 diketone 3c using sodium borohydride pyridine (pyr) yields 1 α -methyl dehydroepiandrosterone 3a.

The following procedures are illustrative for alkylation at carbon-2 and are figuratively illustrated in scheme 2 below.

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1 Methylation of testosterone (1) using lithium
diisopropylamide (LDA) and methyl iodide afforded a mixture
of 2 α - and 2 β -methyl-17 β -hydroxy-4-androsten-3-one (2 & 3).
5 Treatment of the mixture with sodium methoxide in methanol
epimerizes the 2 β -axial methyl to the 2 α -configuration (2).
Acetylation of 2 with acetic anhydride (Ac₂O) and p-toluene sul-
fonic acid (PTSA) in toluene afforded 2 α -methyl-3,17 β -dihydroxy-
3,5-androstadien-3,17-diacetate (4). Treatment of the
10 diacetate (4) with sodium borohydride in 95% ethanol yielded
2 α -methyl-3 β ,17 β -dihydroxy-5-androsten-17-acetate (5).
Protection of the 3-hydroxy group as a tetrahydropyranyl
ether followed by hydrolysis of the 17-acetate yielded
2 α -methyl-3 β ,17 β -dihydroxy-5-androsten-3-tetrahydropyranyl
15 ether 7. Oxidation of the C-17 hydroxy group in 7 followed
by hydrolysis of the tetrahydropyranyl ether with hydro-
chloric acid and aqueous acetone yielded 3 β -hydroxy-2 α -
methylandrost-5-en-17-one (9).

The following is a specific example for the
20 synthesis of 2 α -methyl DHEA.

To a solution of diisopropylamine (5.3 ml, 38 mmol)
in freshly distilled tetrahydrofuran (80 ml) stirred at
-78°C was added n-butyllithium (29.3 ml of 1.3 M in hexane,
38 mmol). This was stirred at -78°C for 30 minutes then
25 warmed to -30° and 17 β -hydroxy-4-androsten-3-one (1)
(5.0 g, 17.3 mmol) in tetrahydrofuran (30 ml) was added
dropwise. After 30 minutes at -30°C iodomethane (4 ml,
80 mmol) was added. The mixture was allowed to slowly
warm to room temperature with stirring, then saturated
30 ammonium chloride solution was added and the product was
extracted with ether. The organic layer was dried and
the solvent removed to give a mixture of isomers 2 & 3
as an oil (5.26 g) which was used in the next step.

1 To a stirred solution of sodium (0.75 g, 32 mmol)
dissolved in methanol (100 ml) was added the epimeric mix-
ture of 2-methyl-17 β -hydroxy-4-androsten-3-one, 2 & 3
(4.93 g, 16.2 mmol) in methanol (100 ml). After 17 hours
5 at room temperature, saturated ammonium chloride solution
was added and most of the solvent was removed in vacuo.
The product was extracted with dichloromethane, washed
with water, dried and the solvent removed to give a gum
(4.86 g) which was purified by column chromatography on
10 silica gel. Elution with hexane ether gave 1.6 g of 2
which crystallized from methanol mp 149-151°C;
 H^1 NMR ($CDCl_3$) δ 5.64 (s, 1, H-4), 3.60 (t, 1, H-17, J=9Hz),
1.24 (s, 3, H-19), 1.13 (d, 3, H-2 methyl, J=6 Hz), 0.83
(s, 3, H-18); MS m/e 302(M^+ , 33), 260(21), 246(29), 28(100).
15

A solution of 2 α -methyl-17 β -hydroxy-4-andro-
sten-3-one (2) (4.86 g, 16.1 mmol) product mixture from
previous step in acetic anhydride (40 ml) and paratoluene
20 sulfonic acid (200 mg) in toluene (100 ml) was refluxed
3 1/2 hours. Pyridine (1 ml) was added and the mixture
was concentrated on a rotary evaporator then partitioned
between methylene chloride and water. The organic layer
was dried and the solvent removed. The product mixture
25 (5.78 g) was separated on a flash silica column to give
2 α -methyl-3,17 β -dihydroxy-3,5-androstadien-3,17-diacetate
(4) 1.81 g (27.4%) crystallized from Et_2O - hexane mp
170-171°C.

30 H^1 NMR ($CDCl_3$) δ 5.57 (s, 1, H-4), 5.40 (m, 1, H-6), 4.55
(t, 1, H-17, J=9Hz), 2.08 (s, 3, 3-acetate), 2.01 (s, 3,
17-acetate), 1.06 (s, 3, H-19), 0.98 (d, 3, 2 methyl,
J=6 Hz), 0.83 (s, 3, H-18); MS m/e 386(M^+ , 3) 358(12),
43(100).
35

1 A suspension of 2 α -methyl-3,17 β -dihydroxy-
3,5-androstadien-3,17-diacetate (4) (1.31 g, 3.4 mmol)
and sodium borohydride (1.3 g) in 95% ethanol (100 ml)
was stirred at room temperature for 3 1/2 hours. The
5 solution was cooled to 0°C and glacial acetic acid was
added, followed by saturated sodium bicarbonate solution.
The product was partitioned between dichloromethane and
water, the organic layer dried, and the solvent removed
to give 1.23 g product mixture which was separated on
10 40 g of flash silica column eluted to give 5, 0.7 g
from ether hexane) mp 179-182°C;
H¹ NMR (CDCl₃) δ 5.27 (m, 1, H-6), 4.62 (t, 1, H-17, J=9Hz),
3.03 (t, 1, H-3, J=9Hz) 2.05 (s, 3, 17-acetate), 1.07
(s, 3, H-19), 1.02 (d, 3, 2-methyl, J=8Hz), 0.83 (s, 3,
15 H-18).

A solution of 2 α -methyl-3 β ,17 β -dihydroxy-5-
androst-17-acetate 5 (1.42 g, 4.1 mmol) dihydropyran (DHP)
(10 ml) and paratoluene sulfonic acid (100 mg) in ether
(50 ml) was stirred at room temperature for 17 hours.
20 The ether solution was washed with saturated sodium
bicarbonate solution then water, dried and solvent
removed to give the product mixture as an oil (1.65 g)
The product was not purified but carried on to the next
step.

25 2 α -Methyl-3 β ,17 β -dihydroxy-androst-5-ene-3-tetra-
hydropyranyl ether 17-acetate, 6, from the previous step
(1.65 g, 3.84 mmol) was dissolved in a solution of 5%
potassium carbonate in 4:1 methanol:water (100 ml) and
refluxed 1.5 hours. Most of the solvent was removed
30 under reduced pressure and the product was partitioned
between chloroform and water. The organic layer was dried
and solvent removed to give 1.45 g of the product 7
which was used on the next step.

1 The product mixture 7 from previous step
(1.45 g, 3.84 mmol) was dissolved in pyridine (10 ml)
and added to the complex formed by mixing chromium
trioxide (2 g) in pyridine (20 ml). This was stirred
5 2 1/2 hours at room temperature then 1:1 ether:benzene
(30 ml) was added and the mixture was filtered through
celite then silica gel. The solvent was removed to
give the product mixture 8, 1.52 g as an oil which
was carried on to the next step.

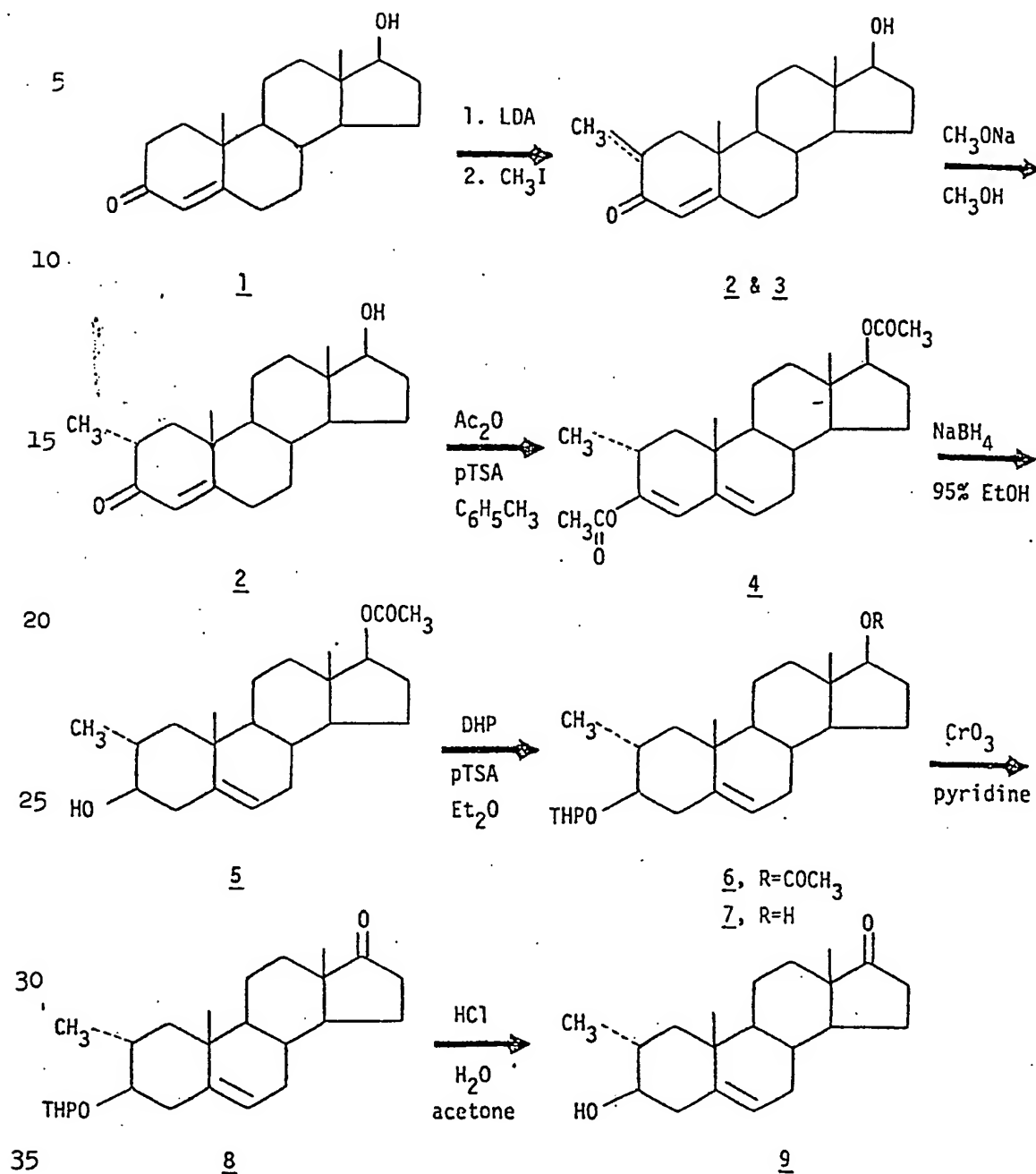
10 A solution consisting of the product mixture 8
from the previous step (1.52 g, 3.94 mmol) and 3N HCl
(2 ml) in acetone (40 ml) was stirred at room tempera-
ture for 3 hours. Saturated sodium bicarbonate solution
was added and the product was extracted with dichloro-
15 methane. The organic layer was dried and the solvent
removed to give 1.17 g product mixture which was separated
on a flash silica column. Elution with 30:70 ether:hexane
gave 3 β -hydroxy-2 α -methyl-androst-5-en-17-one (9) (317 g)
which was crystallized from ether:hexane mp 171.5-173;
20 ¹H NMR(CDCl₃) δ 5.45 (m, 1, H-6), 3.10 (broad m, 1, H-3)
1.13 (s, 3, H-19), 1.07 (d, 3, 2 methyl, J=8Hz), 0.97
(s, 3 H-18).

 As stated before, the above reactions involving
alkylation at carbon-2 are figuratively illustrated in
25 Scheme 2.

30

35

Scheme 2



1 The following procedures are representative
for carbon-3 alkylations, shown figuratively in scheme 3 below.

 Synthesis of dehydroepiandrosterone with a
methyl group replacing the hydroxyl group at carbon-3
5 is shown below in scheme 3. The methyl configuration
at carbon-3 is β , as determined by X-ray analysis.
3 β -Hydroxyandrost-5-en-17-one (10) was iodinated
at carbon-3 with catechol phosphochloridate followed
by iodine. 3 β -Iodoandrost-5-en-17-one (11) was
10 ketalized then alkylated with a mixture of methyl
lithium and cuprous cyanide, in tetrahydrofuran to
yield 3 β -methylandrost-5-en-17-ethylene ketal (13).
Hydrolysis of the ketal afforded 3 β -methylandrost-5-
en-17-one (14).

15

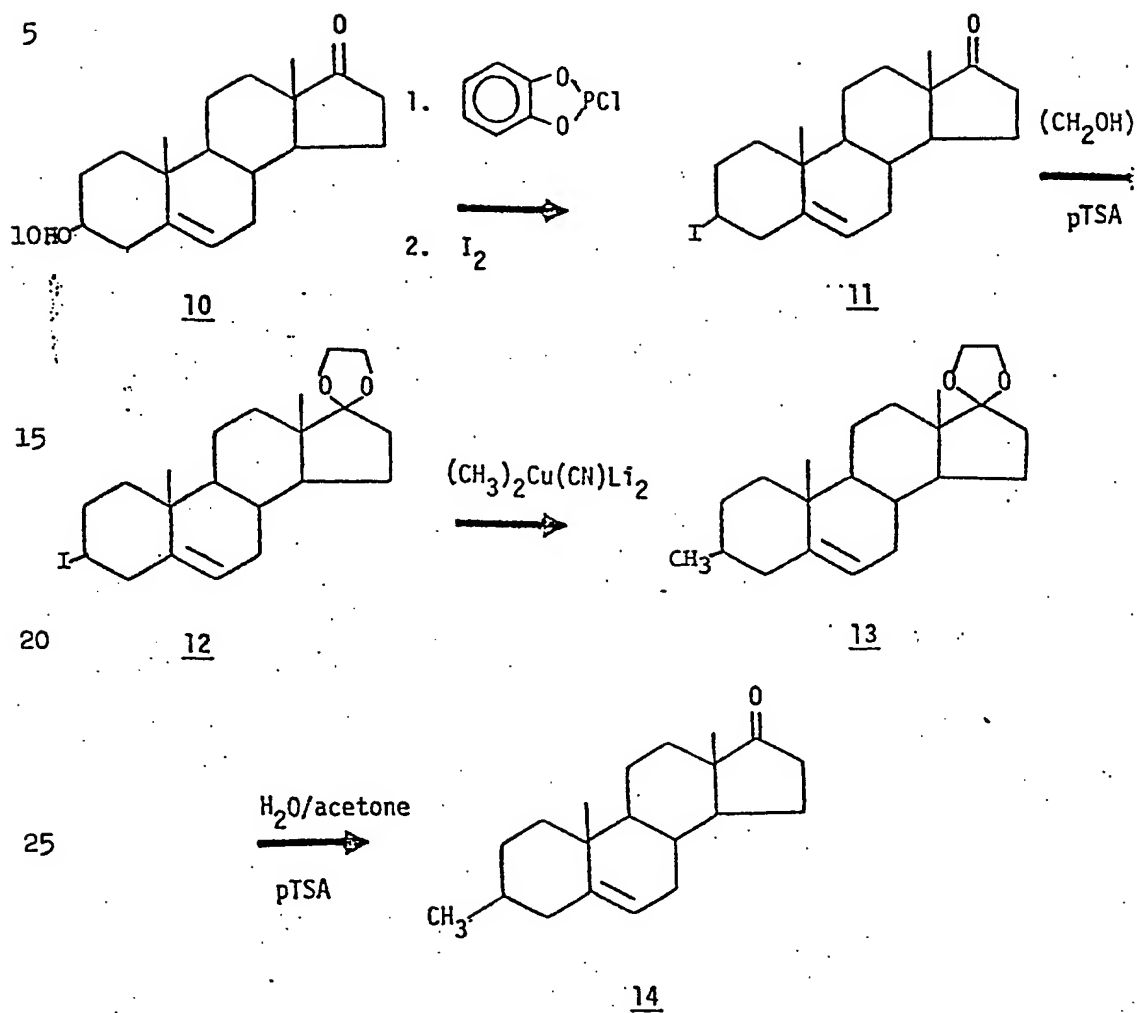
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Scheme 3



- 1 More specifically, 3 β -iodoandroster-5-en-17-one
(11) (11.83g, 29.7 mmol) ethylene glycol (20 ml) and
p-toluene sulfonic acid (200 mg) in benzene (250 ml)
were refluxed under a Dean-Stark trap for 72 hrs. The
5 solution was washed with saturated sodium bicarbonate,
water, then dried over magnesium sulfate. Evaporation
and recrystallization from ether afforded 11.5g (87.3%)
of 3 β -iodoandroster-5-en-17-one 17-ethyleneketal (12):
mp 140-141°C, IR(KBr) 3010, 2940, 1470, 1425, 1375 cm⁻¹
10 ¹H NMR (CDCl₃) δ 5.44 (brd J=6Hz, 1H, H-6) 3.91 (s, 4H,
ketal) 1.07 (s, 3H, C-19 Me) .88 (s, 3H, C-18 Me);
MS (m/e) 442 (M⁺, 1), 380 (35), 315 (57), 253 (67),
227 (11), 105 (24), 99 (100), 91 (35), 55 (27), 41 (33).
Cuprous cyanide (4.465 g, 49.9 mmol) was placed
15 in a dry 500 ml 3 neck round bottom flask equipped with a
magnetic stirrer. The system was flushed with N₂ and dry
THF (30 ml) was added. The suspension was cooled to -78°C
and MeLi 1.5 M (66.5 ml, 99.8 mmol) was added via syringe.
The solution was allowed to warm to 0°C for 5 min., which
20 resulted in a clear tan solution.
After recooling to -78°C, the 3 β -iodo-17-ketal
(3) (7.35 g 16.6 mmol) in 40 ml dry tetrahydrofuran was
added via a syringe and the solution allowed to warm to
room temperature and stirred for 18 hrs. under N₂. The
25 solution was extracted with 100 ml of 90% saturated
NH₄Cl/10% conc. NH₄OH. The organic layer was separated,
dried over MgSO₄ and evaporated to give 6.69 g of crude
product. Chromatography on flash silica (240 g) and elu-
tion with 1% Et₂O/99% hexane gave 6.41 g of colorless
30 crystals. Recrystallization from methanol (200 ml) gave
3 β -methylandroster-5-en-17-one 17-ethyleneketal (4).

1 mp 121-122°C Anal. Calc. C 80.06 H 10.38.

Found C 80.12 H 10.55

IR(KBr) 3010, 2930, 1450, 1430, 1370; ^1H NMR (CDCl_3) δ 5.33 (brd $J=6\text{Hz}$, 1H, H-6) 3.90 (s, 4H, ketal) 1.03 (s, 3H, C-19 Me) .91 (s, 3H, C-18 Me) .97 (d, 3H, C-3 Me); MS (m/e) 330 (M^+ , 16), 316(7), 268(29), 253(22), 239(9), 99 (100), 91(22), 55(27), 41(22).

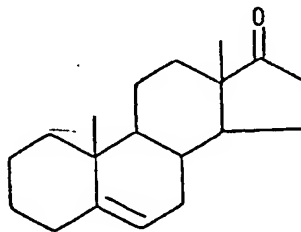
The 3 β -methylandrost-5-en-17-one 17-ethylene-ketal (13) (2.20 g 6.7 mmol) was dissolved in acetone (100 ml). p-Toluene sulfonic acid (100 mg) and H_2O (20 ml) were added and the solution refluxed for 2 hrs. The solution was evaporated, taken up in ether (30 ml), washed with saturated NaHCO_3 , H_2O , then dried over MgSO_4 . The solution was filtered and evaporated to give a colorless solid which was recrystallized from methanol to give 3 β -methylandrost-5-en-17-one (14) colorless plates 1.17 g (61%).

mp 148-150°C; IR(KBr) 3010, 2910, 1740, 1455, 1430, 1365; ^1H NMR (CDCl_3) δ 5.41 (brd, $J=6\text{Hz}$, 1H, H-6) 1.11 (s, 3H, C-19 Me) 0.99 (s, 3H, C-18 Me) 1.07 (d, 3H, C-3 Me); MS (m/e) 286 (M^+ , 58) 271(51), 229 (31), 159 (36), 105 (72), 91 (95), 79 (89), 55 (9), 41 (100).

Anal. Calc. C 83.85 H 10.55

Found C 83.66 H 10.65

25 Androst-5-en-17-one 15 (Desoxy DHEA)



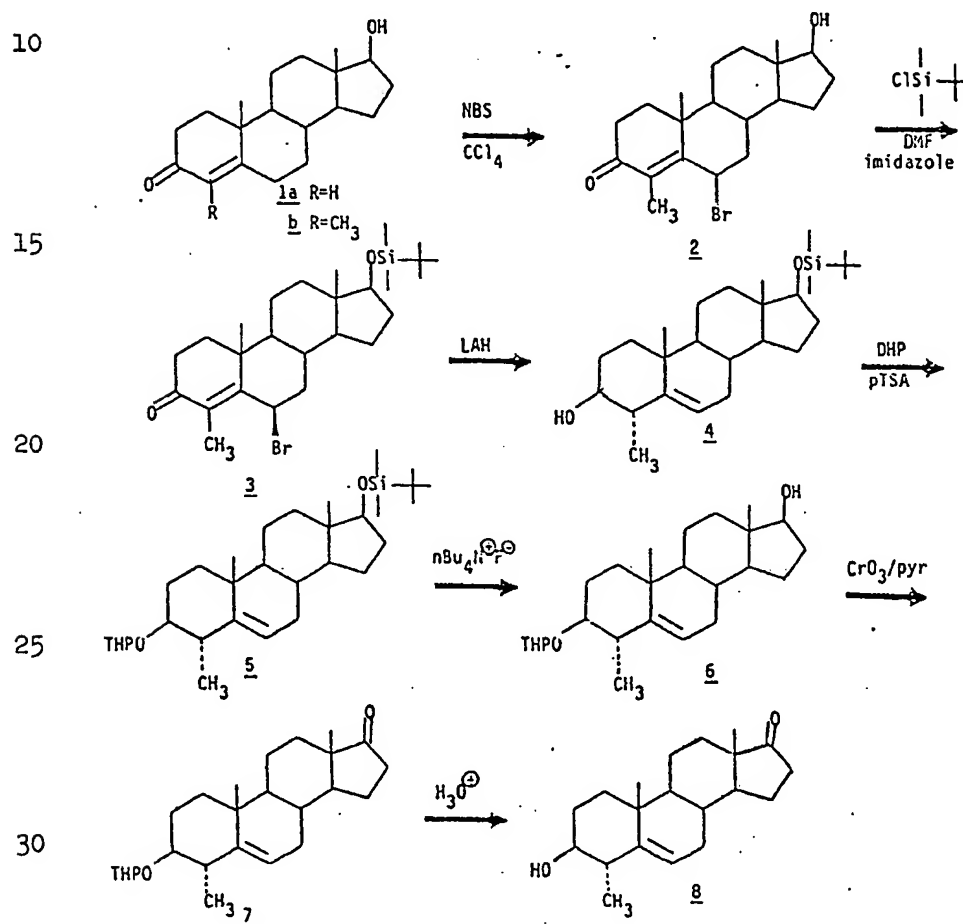
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1 Androst-5-en-17-one (15) mp 106° is synthesized in accordance with T. Nambara and H. Takahashi, Chem. Pharm. Bull. Jap., 1970, 18, 2309 m.p. 108-109°C.

5 A procedure for carbon-4 alkylation and the synthesis of 4 α -methyl DHEA is given in Scheme 2.

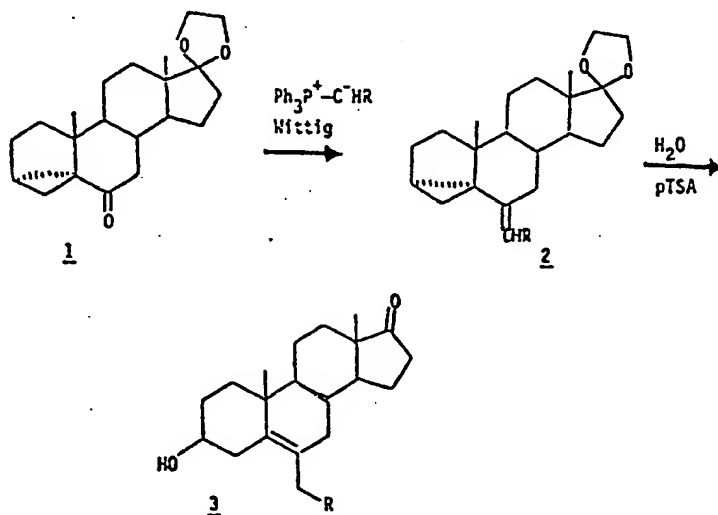
Scheme 4



With reference to Scheme 4, alkylation of testosterone 1a using potassium t-butoxide and methyl iodide according to the method of Atwater yielded 4-methyltestosterone 1b. Allylic bromination of 4-methyltestosterone using N-bromo-succinimide in carbon tetrachloride yields the 6 β -bromo-4-methylandrosta-4-en-17 β -ol-3-one 2. Protection of the C-17 alcohol as its t-butyldimethyl silyl derivative yields 3. Lithium aluminum hydride reduction of the ketone in 3 with concomitant double bond migration and loss of bromide should yield 4. Protection of the C-3 alcohol as a tetrahydropyranyl ether, followed by deprotection and oxidation of the C-17 alcohol should yield the C-17 ketone 7. Removal of the C-3 tetrahydropyranyl ether should yield 4 α -methyl dehydroepiandrosterone 8.

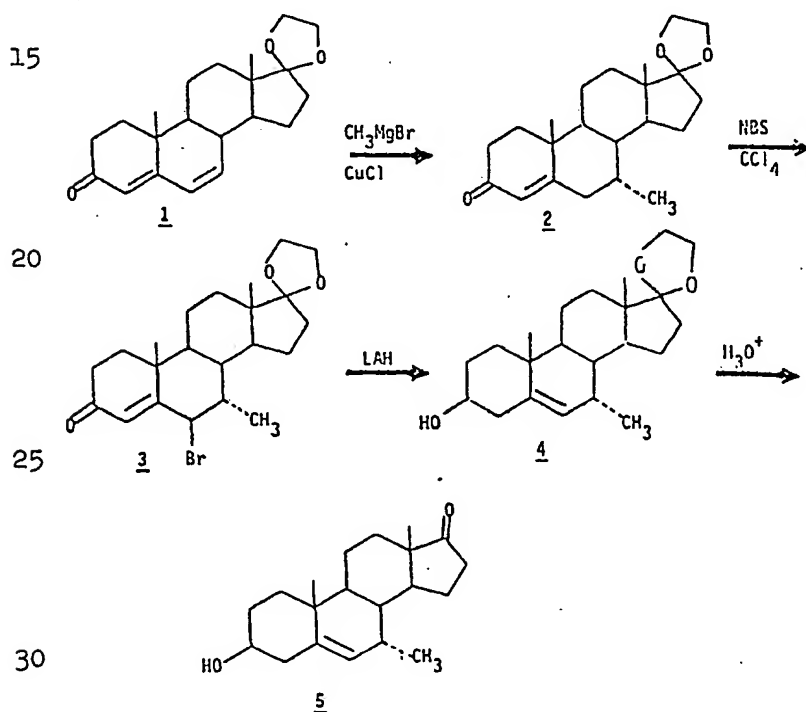
ALKENYLATION AND ALKYLATION AT CARBON-6

Steroids may be alkylated at carbon-6 using the method of U. Stache and W. Fritsch Liebigs Analen 1966, 697, 204.



1 $3\alpha,5$ -Cyclosteroids such as $3\alpha,5$ -cyclo- 5α -androstan-6,17-dione 17 ketal 1 are readily available by solvolysis of steroidal 5-ene- 3β -tosylates and mesylates followed by oxidation of the C-6 hydroxyl group, 5 Methylenation of 1 affords 6-methylene- $3\alpha,5$ -cyclo- 5α -androstan-17-one 17-ketal 2 (R=H). Treatment of 2 with aqueous acid results in the addition of water and the formation of 3β -hydroxy-6-methylandrost-5-en-17-one, 3 (R=H). Alkenylated derivatives of 3 may be synthesized starting with the appropriated substituted Wittig reagent, such as $\text{Ph}_3\text{P}^+\text{---CH}^-\text{CH=CH}_2$.

Alkylation at C-7

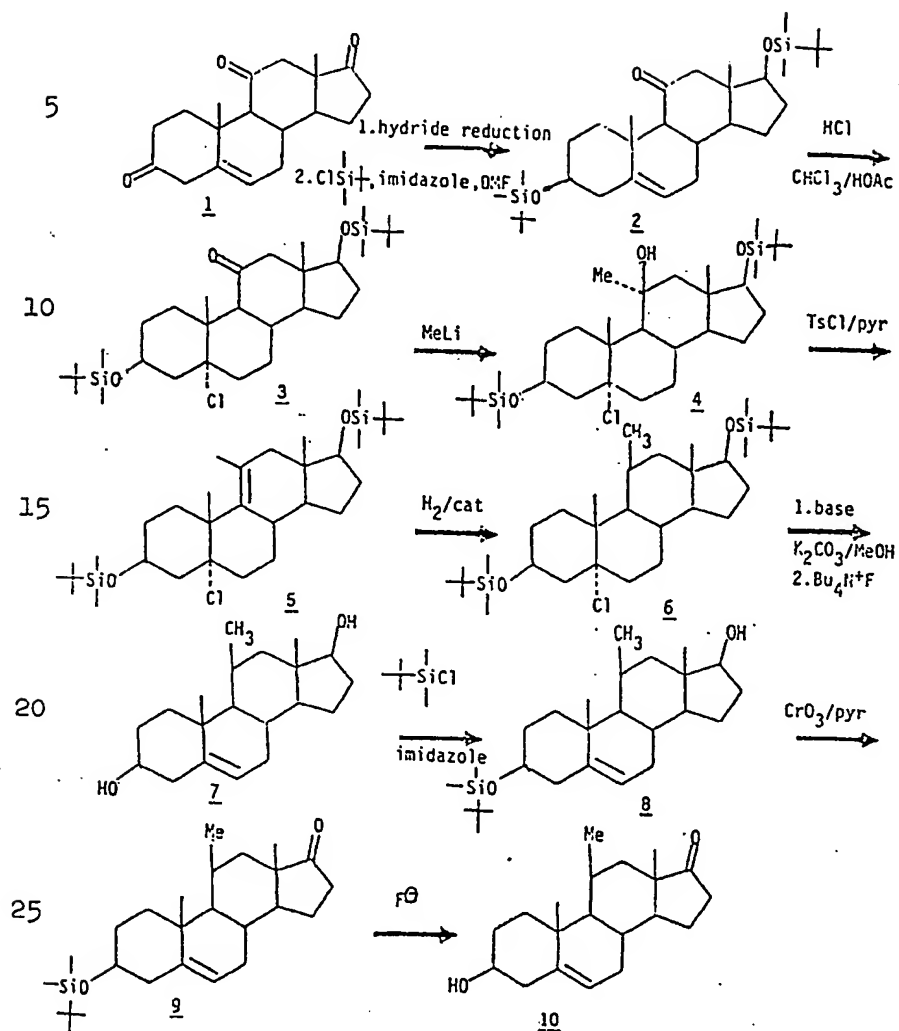


1 Alkylation of androsta-4,6-dien-3,17-dione 17
ketal 1 with methyl magnesium bromide in the presence of
cuprous chloride, proceeds via conjugate addition to
yield 7 α -methylandrost-5-en-3,17-dione 17 ketal 2. Ally-
5 lic bromination of 2 using N-bromosuccinimide in carbon
tetrachloride yields the 6 β -bromo-7 α -methylandrost-4-en-
3,17-dione 17 ketal 3. Lithium aluminum hydride reduc-
tion of the ketone in 3 with concomitant double bond
migration and loss of bromide should yield 4. Depro-
10 tection of the C-17 ketone with aqueous acid yields
3 β -hydroxy-7 α -methylandrost-5-en-17-one, 5. Higher
homologues may be synthesized using the substituted
Grignard reagent i.e. R=CH₃, C₂H₅, C₃H₇. The 7 β -epimer
can be synthesized by treatment of 2 with DDQ--dichloro-
15 dicyanoquinone to generate another olefin at C-7. Cata-
lytic reduction of this olefin should occur from the
 α face of the steroid to yield the 7 β -methyl steroid
i.e. 7 β -methylandrost-5-en-3,17-dione 17 ketal. Follow-
ing the same sequence as above yields 3 β -hydroxy-7 β -
20 methylandrost-5-en-17-one.

25

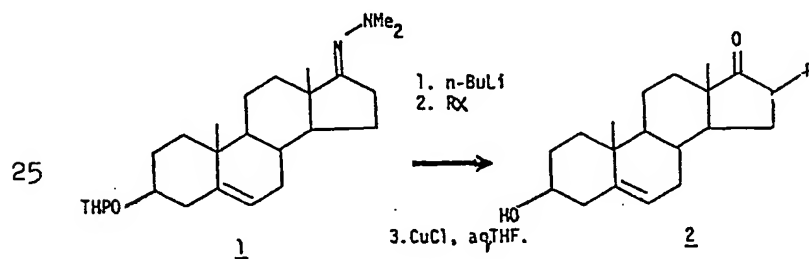
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1 Alkylation at Carbon-11

1 Due to the hindered nature of the C-11 ketone, selective reduction of androst-5-en-3,11,17-trione 1 with hydride should yield the C-3, C-17 dihydroxy steroid 2a, R=H which is protected as its bis(dimethyl-tert-butylsilyl)ether 2b R=Si(CH₃)₂t-Bu. Addition of hydrogen chloride across the C-5 olefin affords 5 α -chloro-3 β ,17 β -dihydroxyandrost-5-en-11-one 3,17-bis(dimethyl-t-butylsilyl) ether 3. Alkylation with methyl lithium proceeds from the less hindered α face to yield 5 α -chloro-11 α -methylandrostan-3 β ,11 β ,17 β -triol-3,17-bis(dimethyl-t-butylsilyl) ether 6. Treatment of the chloro silyl ether 6 with base followed by tetrabutyl ammonium fluoride affords 11 β -methylandrost-5-en-3 β ,17 β -diol 7. Selective silylation yields 11 β -methylandrost-5-en-3 β ,17 β -diol 3-dimethyl t-butylsilyl ether 8. Oxidation of the C-17 alcohol in 8 yields 9 and deprotection of the 3-alcohol yields 11 β -methylandrost-5-en-3 β -ol-17-one 10. (11 β -methyl DHEA).

20 Alkylation at Carbon-16



30

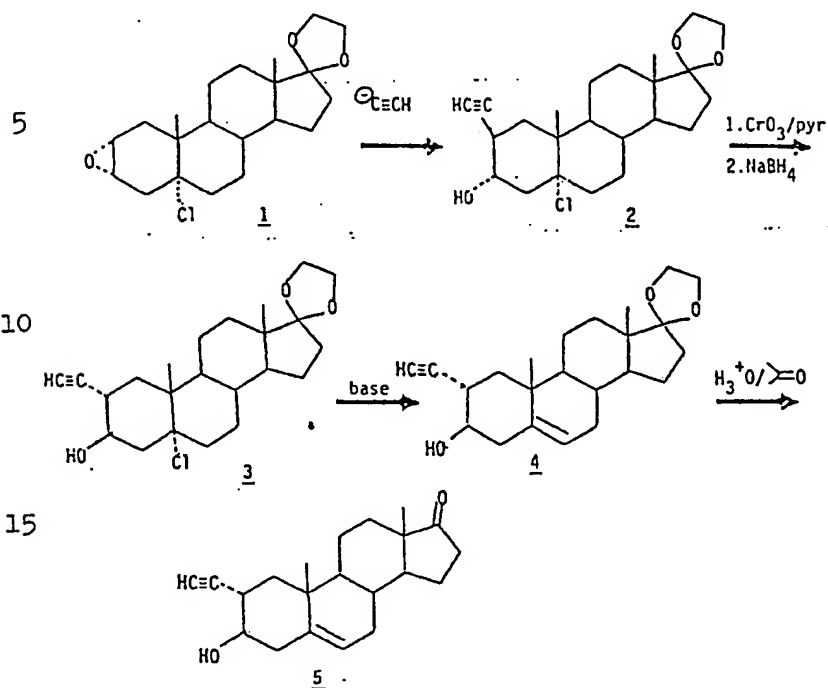
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Alkylation of the 17-ketodimethylhydrazone of DHEA 3-tetrahydropyranyl ether using n-butyl lithium as the base followed by an alkyl halide RX, afforded the 16 α -alkylated steroid. Hydrazone cleavage with cuprous chloride in aqueous tetrahydrofuran led to regeneration of the C-17 ketone and concomitant cleavage of the tetrahydropyranyl ether resulting in the 16 α -alkyl-3 β -hydroxy-androst-5-en-17-one 2. Similarly, 3- β , 16 α -dimethyl-androst-5-en-17-one may be prepared by alkylation of 3- β , methyl androst-5-en-17-one using this procedure to introduce the 16 α -methyl group, as illustrated by the following procedure:

Diisopropyl amine (1.165g, 11.5mmol) was dissolved in dry tetrahydrofuran (30ml) at -78°C under N₃. n-Butyl lithium (4.44ml of a 2.6M solution in hexane, 11.5 mmol) was added via syringe and the solution warmed to -23°C (CO₂, CCl₄) for .25h. 3 β -methyl androst-5-ene-17-one (3.0g, 10.4 mmol) in dry tetrahydrofuran (30ml) was added via syringe and the solution stirred for .25h. Methyl iodide (7.0g, 49.33 mmol) in dry tetrahydrofuran (30ml) was added dropwise and the mixture stirred at room temperature for 1.5 h. The solution was quenched with saturated ammonium chloride and the organic layer separated, dried over magnesium sulfate, filtered and evaporated. The residual solid was chromatographed on flash silica gel (120g) and eluted with 1/99 (v/v) ether hexane to give 3 β ,16 α -dimethyl androst-5-ene-17-one (2.3g, 74%) M.P. 109-110°C (recrystallized from methanol). NMR(CDCl₃) δ 5.29 (brd, J=5Hz, 1H, H-6), 2.52 (m, 1-H, H-16) 1.07 (d J=8Hz, 3H, C-16Me), .99 (s, 3H, C-19Me), .91 (s, 3H, C-18Me). IR(kBr) 2900, 1730, 1450, 1430, 1370. Anal. calc. for C₂₁H₃₂O, C-83.93, H-10.73. Found C-83.79, H-10.52. MS 300M+(100) 285(62), 282(2), 272(12), 267(17), 229(20), 217(30), 159(17).

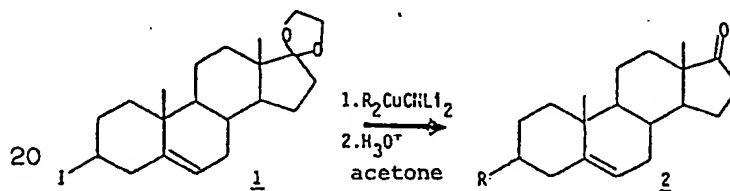
The following procedures are illustrative of alkenylation and alkynylation at Carbon-1.

- Alkenylation ($-\text{CH} = \text{CHR}$) may be effected using the vinyl analogue of the organocuprate reagent i.e.
- 5 ($\text{CHR}=\text{CH}$)₂ CuLi as in Scheme 1 above. Alkynylation ($-\text{C}\equiv\text{C}-\text{R}$) using dialkynyl lithium cuprate is possible but this reagent is extremely sluggish. However, using a tri-n-butylstannyl ethylene which may be oxidized by lead tetraacetate to an acetylene (E. J. Corey and
- 10 R. H. Wollenberg, J. Amer. Chem. Soc., 1974, 96, 5581) affords a convenient method for the introduction of an acetylde group. Thus using 2-tri-n-butylstannyl ethenyl 1'-pentynyl lithium cuprate ($[\text{C}_3\text{H}_7\text{C}\equiv\text{C}-\text{Cu}-\text{CH}=\text{CHSn nBu}_3]/\text{Li}$), tri-n-butylstannylethylene is added to
- 15 the steroid. Oxidation using lead tetraacetate proceeds with the loss of tin and affords the corresponding acetylde. Also aluminum acetylides undergo conjugate addition to enones.

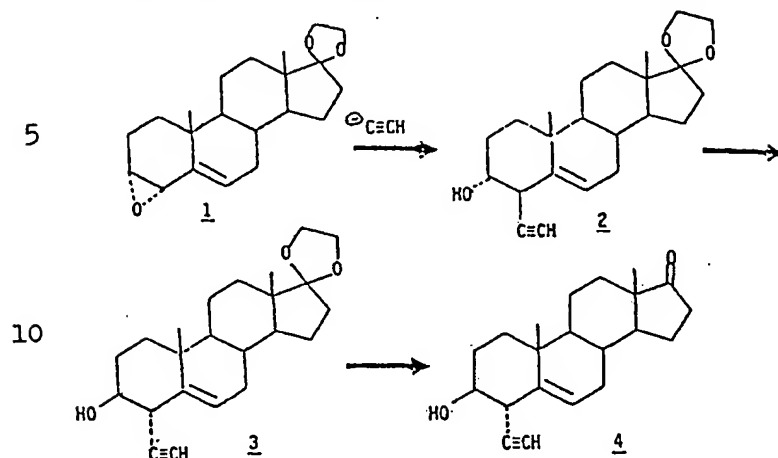
1 Alkenylation and Alkynylation at Carbon-2

1 Reaction of 5 α -chloro-2 α ,3 α -epoxyandrostan-17-one 17 ketal 1 with lithium acetylide ethylene diamine complex yields 5 α -chloro-2 β -ethynylandrostan-3 α -ol-17-one 17-ketal 2. Epimerisation of the C-3 alcohol by
 5 oxidation to the C-3 ketone (chromium trioxide/pyridine) and reduction with sodium borohydride affords 5 α -chloro-2 β -ethynylandrostan-3 β -ol-17-one 17-ketal 3. Deprotection of the C-5 olefin and 17-ketone by treatment first with base (K_2CO_3 in methanol) followed by aqueous acid
 10 yields 2 α -ethynyl-3 β -hydroxyandrost-5-en-17-one 5. The 2 α -ethenyl steroid can be synthesized from the ethynyl derivative by careful catalytic reduction with Lindlar catalyst to yield 2 α -ethenyl-3 β -hydroxyandrost-5-en-17-one.

15 Alkenylation and Alkynylation at Carbon-3



Reaction of 3 β -iodoandrost-5-en-17-one 17-ketal 1 with the organo cuprate reagent $(R^1CH=CH)_2Cu(C\equiv N)Li_2$
 25 generated from the appropriate vinyl lithium reagent and cuprous cyanide, should yield the 3 β -alkenylandrost-5-en-17-one 2 ($R=CH=CHR^1$) following removal of the C-17-ketal. Similarly, reaction of 1 with the tri-n-butyl stannyl derivative $R^1=nBu_3Sn$ yields upon oxidation with lead
 30 tetraacetate and hydrolysis of the C-17 ketal, 3 β -ethynyl-androst-5-en-17-one 2 ($R=C\equiv CH$).

1 Alkenylation and Alkynylation at Carbon-4

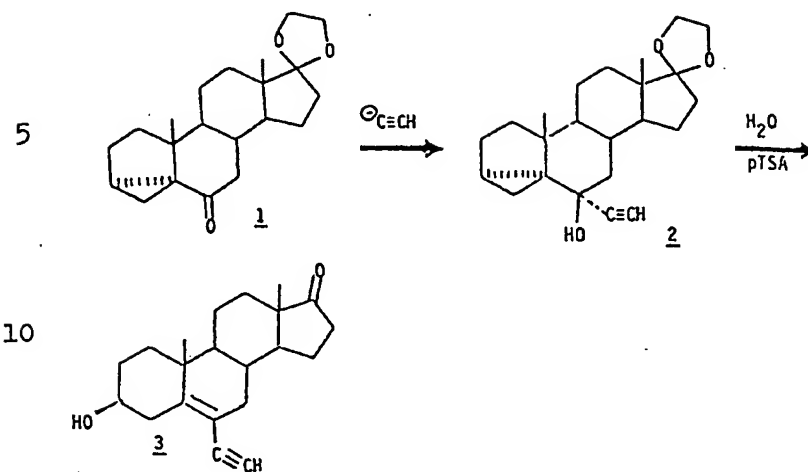
15 Reaction of 3 α ,4 α -epoxyandrost-5-en-17-one-17-ketal 1 with lithium acetylide diethylamine complex affords 4 β -ethynyl-3 α -hydroxyandrost-5-en-17-one-17-ketal 2. Epimerisation of the C-3 alcohol by oxidation to the C-3 ketone with chromium trioxide/pyridine followed by

20 reduction with sodium borohydride affords 4 β -ethynyl-3, β -hydroxyandrost-5-en-17-one-17-ketal 3. Careful hydrolysis of the C-17 ketal affords 4 α -ethynyl-3 β -hydroxyandrost-5-en-17-one, 4.

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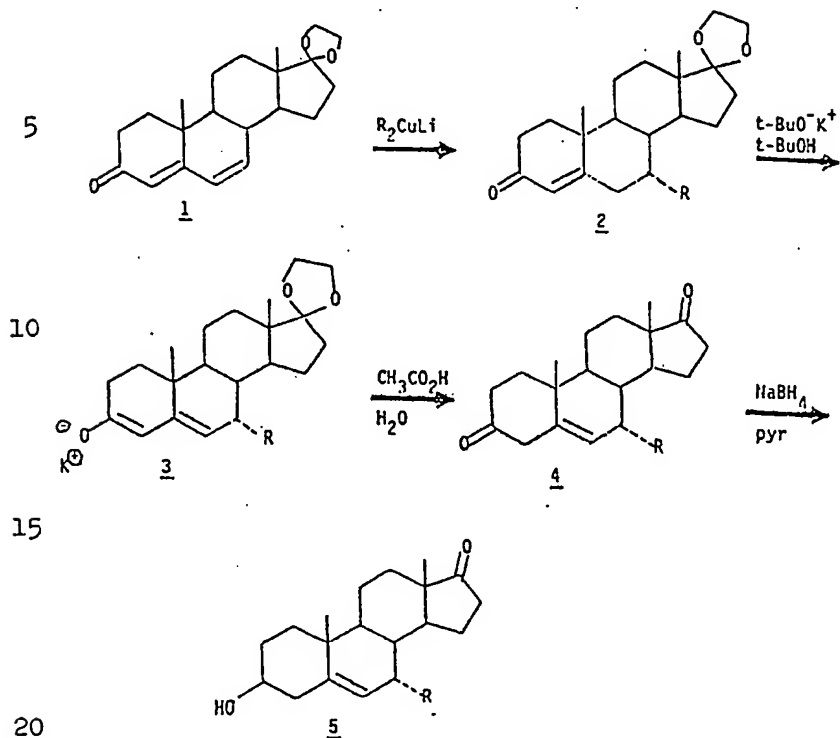
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1 Alkynylation at Carbon-6

15 Treatment of 3 α ,5-cyclo-5-androstan-6,17-
dione 17-ketal 1, with lithium acetylide diethyl
amine complex yields 6 α -ethynyl-6 β -hydroxy-3 α ,5-
cyclo-5 α -androstan-17-one 17-ketal 2. Reaction of 2
with aqueous acid yields 6-ethynyl-1 β -hydroxyandrost
20 5-en-17-one, 3.

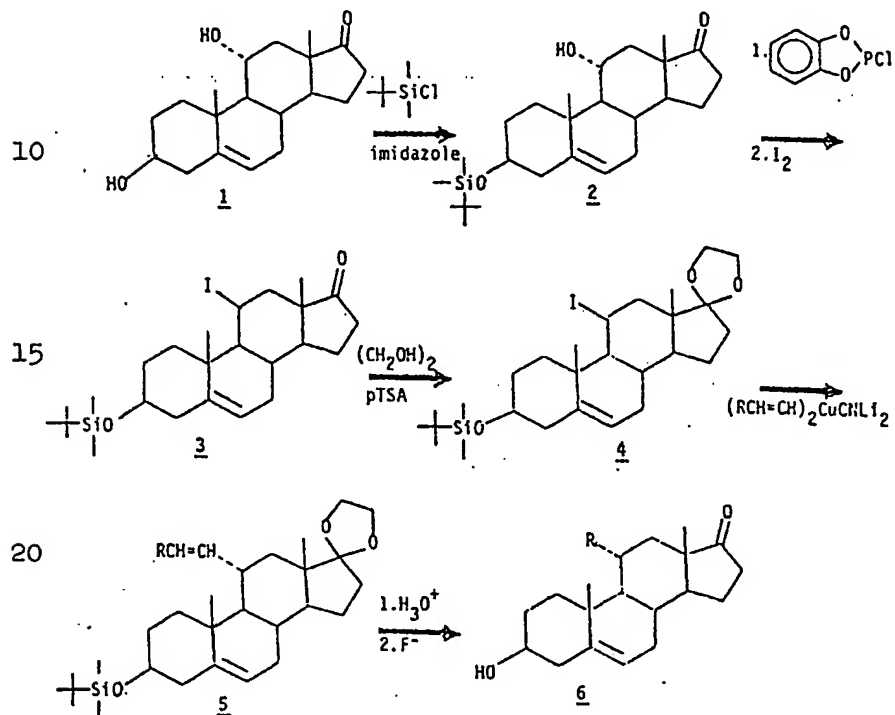
1 Alkenylation and Alkynylation at Carbon-7



Alkenylation and alkynylation of androsta-4,6-dien-3,17-dione 17-ketal 1 with $(\text{CHR}=\text{CH})_2\text{CuLi}$ yields the 7 α -alkenyl steroid 2. Treatment of 2 with potassium t-butoxide in t-butanol yields the dienolate 3 which upon protonation with acetic acid yields 7 α -alkenylandrost-5-en-3,17-dione 4. Selective reduction of the C-3 ketone using sodium borohydride in pyridine yields 3 β -hydroxy-7 α -alkenyl-androst-5-en-17-one, 5 ($\text{R}=\text{CH}=\text{CHR}^1$). Alkynylation may be effected using 2-tri-n-butylstannyl ethenyl 1'-pentynyl lithium cuprate ($[\text{C}_3\text{H}_7\text{C}\equiv\text{C}-\text{Cu}-\text{CH}=\text{CHSnBu}_3]\text{Li}$), as the alkynylating reagent. The tri-n-butylstannylethylene added by this reagent is oxidized using lead tetraacetate

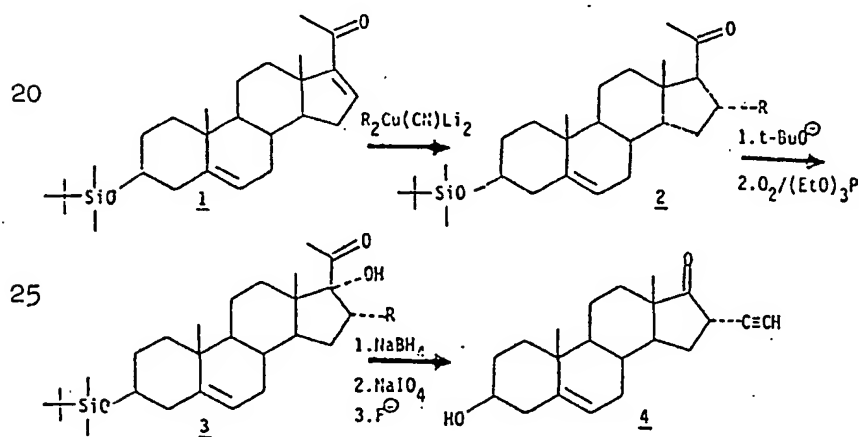
1 resulting in the loss of tin and the formation of an acetylide, namely 3 β -hydroxy-7 α -alkynylandrost-5-en-17-one, 5 ($R=C\equiv CH$).

5 Alkenylation and Alkynylation at Carbon-11



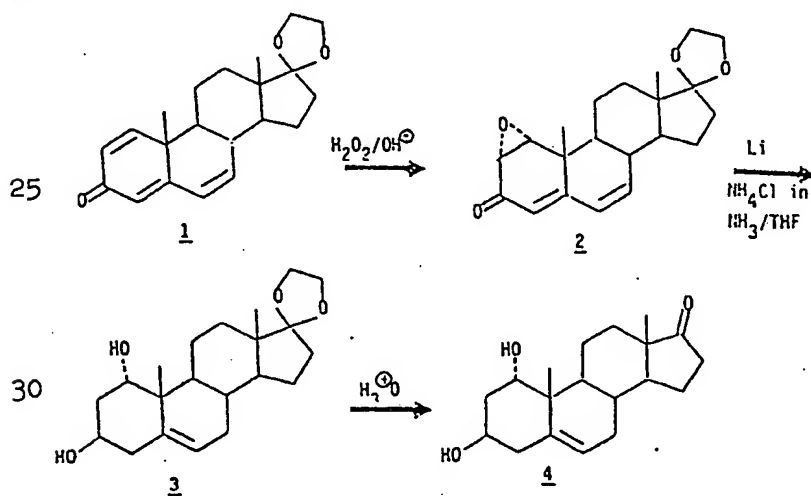
1 Reaction of the less hindered 3 β -hydroxyandrost-
 5-en-17-one 1 with t-butyldimethylsilyl chloride yields
 the 3 β -t-butyldimethylsilyl ether 2. Treatment of this
 first with catechol phosphochloridate followed by dis-
 5 placement with iodine yields 3 β -hydroxy-11 β -iodoandrost-
 5-en-17-one dimethyl-t-butylsilyl ether 3. Protection
 of the C-17 ketone as the 1,3-dioxolane 4 followed by
 alkenylation using dialkenyl dilithio cyano cuprate,
 (RCH=CH)₂ CuCNLi₂ yields 11 α -alkenyl-3 β -hydroxyandrost-
 10 5-en-17-one t-butyldimethylsilyl ether 5. Deprotection
 of the C-17 ketone and 3 β alcohol affords 11 α -alkenyl
 3 β -hydroxyandrost-5-en-17-one 6. If 6 has R=2'-tri-n-
 butylstannyl ethenyl then lead tetraacetate oxidation
 affords 11 α -alkynyl 3 β -hydroxyandrost-5-en-17-one, 6,
 15 (R=C \equiv CH).

Alkynylation and Alkenylation at Carbon-16

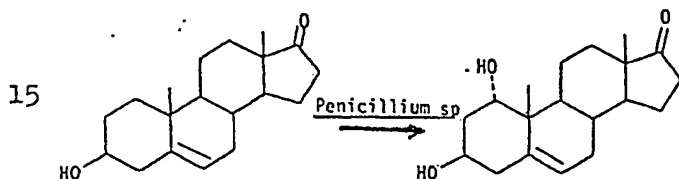


1 Michael addition of a suitably substituted
 organo copper reagent such as 2-tri-n-butylstannyl
 ethenyl 1'-pentynyl lithium cuprate ($[\text{C}_3\text{H}_7\text{C}\equiv\text{C}-\text{Cu}-\text{CH}=\text{CH}$
 $\text{Sn nBu}_3]\text{Li}$) to 3 β -hydroxypregna-5,16-dien-20-one 3-t-
 5 butyl dimethylsilyl ether 1 yields a 16 α -tri-n-butylstannyl
 ethylene (2, $\text{R}=\text{CH}=\text{CHSn nBu}_3$). Lead tetraacetate oxidation
 proceeds with the loss of tin and yields the correspond-
 ing acetylide. Treatment of 2 with t-butoxide followed
 by oxygen to generate a C-16 α -hydroperoxide which is
 10 reduced by triethylphosphite to 16 α -ethynyl-3 β ,17 α -dihy-
 droxy-pregna-5-en-20-one 3-t-butyl dimethylsilyl ether 3.
 Reduction of the C-20 ketone to an alcohol followed by
 cleavage of the diol with sodium periodate and depro-
 tection of the 3 β -hydroxyl group with fluoride, yields
 15 16 α -ethynyl-3 β -hydroxyandrost-5-en-17-one, 4. Careful
 reduction of the acetylene in 4 should afford the 16 α -
 vinyl substituted steroids. Higher homologues of these
 substituents may be synthesized via similar routes.

The following procedures illustrate hydroxy-
 20 lation at Carbon-1, 2, 4, 7, 11 or 16.



1 Alkaline hydrogen peroxide epoxidation of
androsta-1,4,6-triene-3,17-dione 17-ketal 1 with basic
hydrogen peroxide yields the 1 α ,2 α -epoxide 2. Treat-
ment of 1 α ,2 α -epoxyandrosta-4,6-dien-3,17-dione 17-ketal
5 2 with a large excess each of lithium metal and ammonium
chloride in ammonia-tetrahydrofuran (1:1) at reflux
leads to 1 α ,3 β -dihydroxyandrosta-5-en-17-one 17-ketal 3.
Hydrolysis of the ketal affords 1 α ,3 β -dihydroxyandrosta-
5-en-17-one, 4. Also, fermentation of DHEA with peni-
10 cillium aspergillus affords 4, i.e. penicillium asper-
gillus may be able to 1 α -hydroxylate other substrates.



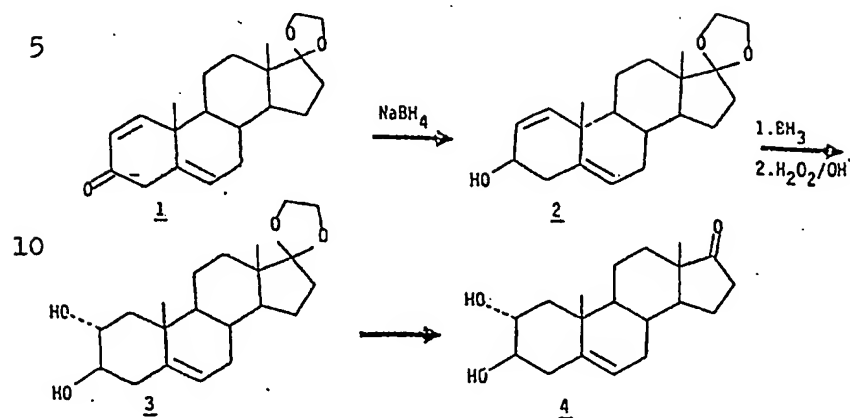
20 Dodson, R.M., Goldkamp, A.M., and Muir, R.D., JACS, 1957,
79, 3921.

Dodson, R.M., Goldkamp, A.M., and Muir, R.D., JACS, 1960,
82, 4026.

25 Penicillium hydroxylates DHEA at C-1 in the
 α -position. Therefore, other substrates that look like
DHEA should be hydroxylated at C-1 by this enzyme.

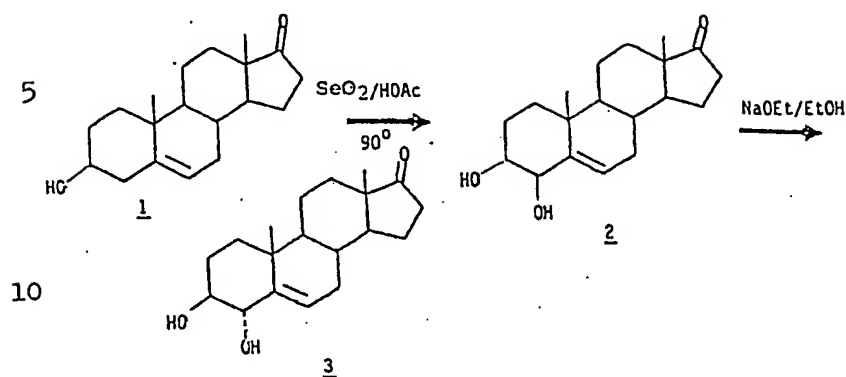
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1 C-2 Hydroxylation2 α ,3 β -dihydroxyandrosta-5-en-17-one

Reduction of androsta-1,5-dien-3,17-dione-17-ketal 1 with sodium borohydride yields 3 β -hydroxyandrosta-1,5-diene-17-one 17-ketal 2. Hydroxylation of the C-1 double bond by hydroboration followed by oxidation with alkaline hydrogen peroxide affords 2 α ,3 β -dihydroxyandrosta-5-en-17-one 17-ketal 3. Deprotection of the C-17 ketone with aqueous acid yields 2 α ,3 β -dihydroxyandrosta-5-en-17-one, 4.

1
Carbon-4 Hydroxylation



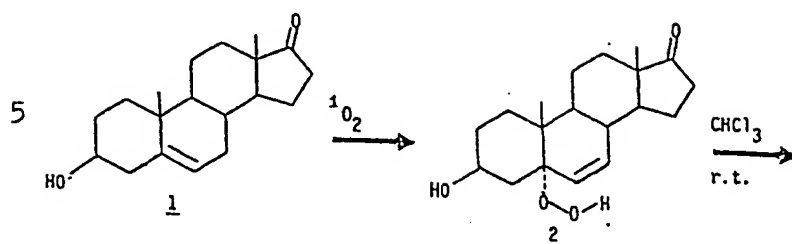
15 Selenium dioxide oxidation of 3β-hydroxyandrost-5-en-17-one yields 3β,4β-dihydroxyandrost-5-en-17-one 2. The axial C-4 alcohol may be epimerized to the equatorial position by reaction with sodium ethoxide in ethanol to yield 3β,4α-dihydroxyandrost-5-en-17-one, 3.

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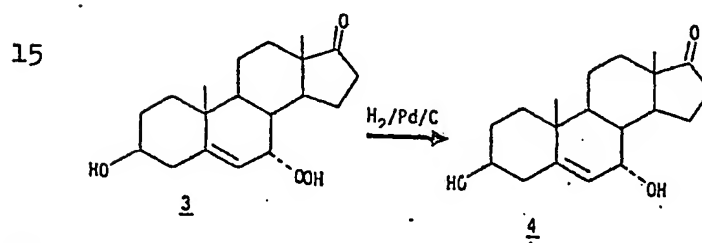
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1 Carbon-7 Hydroxylation

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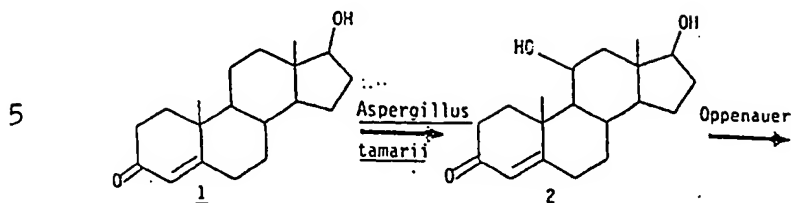


25 3β-Hydroxyandrost-5-en-17-one (DHEA) 1 reacts with singlet oxygen to yield 5α-hydroperoxy-3β-hydroxyandrost-6-en-17-one 2. This hydroperoxide undergoes a rearrangement when in chloroform solution to yield 7α-hydroperoxy-3β-hydroxyandrost-5-en-17-one, 3: Catalytic reduction of the hydroperoxide yields 3β,7α-dihydroxyandrost-5-en-17-one, 4.

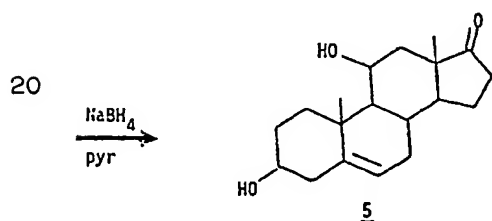
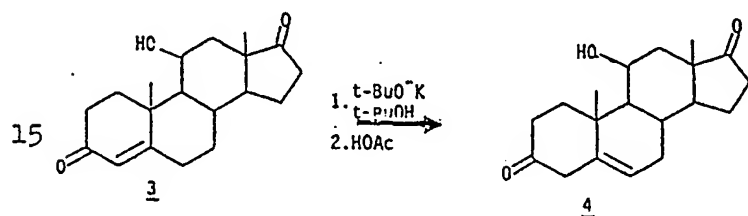
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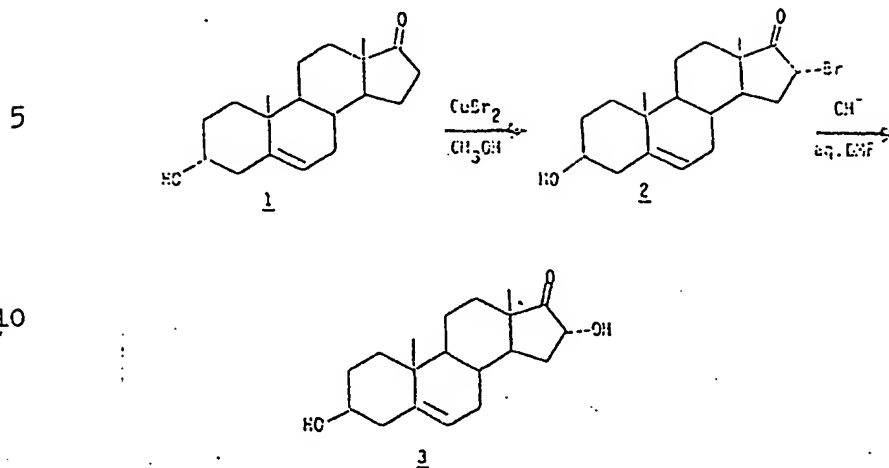
1 Carbon-11 Hydroxylation



10 D.R. Brannon, J. Martin, A.C. Ochlschlager, N.N. Durham,
and L.H. Zalkow, J. Org. Chem. 1965. 30, 760.



Hydroxylation of testosterone 1 at Carbon-11
25 using Aspergillus tamarii affords 11β,17β-dihydroxyan-
drost-4-en-3-one 2. Oppenauer oxidation of 2 oxidizes
the 17β-alcohol in the presence of the hindered 11β-
hydroxyl group to yield 11β-hydroxyandrost-4-en-3,17-dione,
3. Migration of the double bond out of conjugation by
30 treatment with potassium t-butoxide followed by protona-
tion with acetic acid yields 11β-hydroxyandrost-5-en-3,
17-dione 4. Selective reduction of 4 yields 3β,11β-dihy-
droxyandrost-5-en-17-one, 5.

1 Hydroxylation at Carbon-16

15 Bromination of DHEA (1) with cupric bromide yields 16α-bromo-DHEA, 2. Treatment of the bromo ketone 2 with sodium hydroxide in aqueous dimethylformamide gave 3β,16α-dihydroxyandrost-5-en-17-one, 3. See M. Numazawa, M. Nagaoka, Y. Osawa, J. Org. Chem. 1982, 47, 4024. Similarly 3-β-methyl-16α-hydroxy androst-5-en-17-one may be prepared by hydroxylation of 3-β methyl androst-5-en-17-one using this procedure to introduce the 16α-hydroxy group, as illustrated by the following procedure:

20

25 To prepare 3β-methyl-16α-bromo-androst-5-ene-17-one (Ref: E. R. Glazier, J. Org. Chem. (1962) 27 2937; M. Numazawa & Y. Osawa, J. Org. Chem. Steroids (1978) 32, 519; M. Numazawa, M. Nagaoka & Y. Osawa, J. Org. Chem. (1982), 47 4024).

30 3β-methyl androst-5-ene-17-one (4.0g, 14 mmol) and CuBr_2 (9.4g, 42mmol) were dissolved in methanol (250ml) and refluxed for 24h. The hot solution was filtered to remove the white precipitate and the filtrate cooled to

35

-43a-

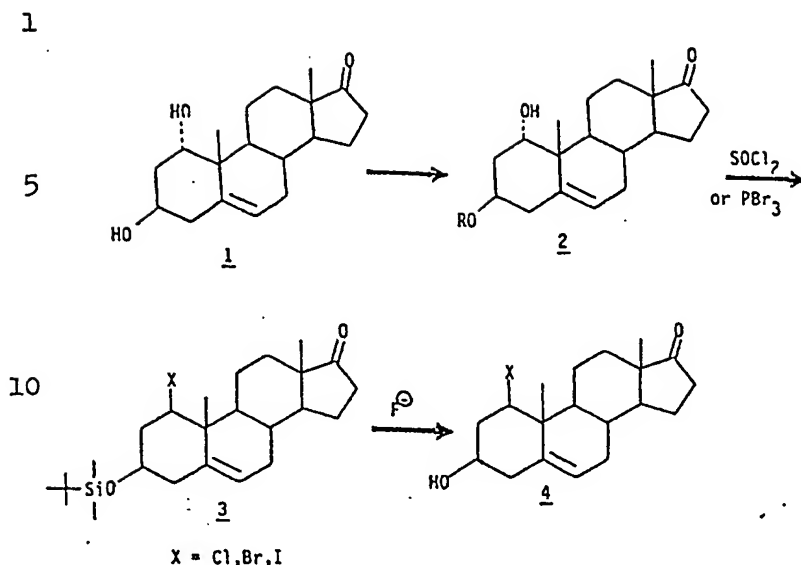
1 yield 3.1g (61%) 3,4-methyl-16 α -bromo androst-5-ene-17-one.
An analytical sample was prepared by passing an ether
solution of the steroid through a small plug of neutral
alumina. Evaporation and recrystallization from methanol
5 gave white needles, M.P. 193-195°C. Anal. calc. for
C₂₀H₂₉OBr, C-65.7, H-8.0. Found C-65.54, H-8.11 NMR
(CDCl₃) δ 5.30 (brd, 1H, H-6), 4.52 (t, 1H, 16 β -H) .98
(s, 3H, C-19Me), .90 (s, 3H, C-18Me) IR(KBr) 2910, 1735,
1445, 1365, 1020.

10 3 β -methyl-16 α -bromo androst-5-ene-17-one
(1g, 2.74 mmol) was dissolved in dimethylformamide (90ml).
Sodium hydroxide (165 mg, 4.1 mmol) in water (10ml) was
added and the solution stirred for 2 h. at room tempera-
ture. The solution was poured into 1% HCl (200 ml) and
15 extracted with ethyl acetate (2 X 50 ml). The organic
layer was washed with 5% sodium bicarbonate, water, then
dried over magnesium sulfate and filtered. Evaporation
gave a pale yellow solid which was chromatographed on
flash silica gel and eluted with ether/hexane (10/90).
20 Recrystallization from ether gave 3 β -methyl-16 α -hydroxy
androst-5-ene-17-one (0.4g, 50%). M.P. 166-168°C. Anal.
calc. for C₂₀H₃₀O₂, C-79.42, H-9.99. Found C-79.24,
H-10.04 NMR (δ -6-DMSO) δ 5.30 (brd, 1H, H-6), 4.38 (t, 1H,
16 β -H) [IR(KBr) 3440, 2900, 1735, 1445, 1365, 1010.]
25 2.0-1.85 (complex).

The following procedures are representative of
procedures for halogenation at Carbon-1, 2, 3, 4, 6, 7,
11 or 16.

30

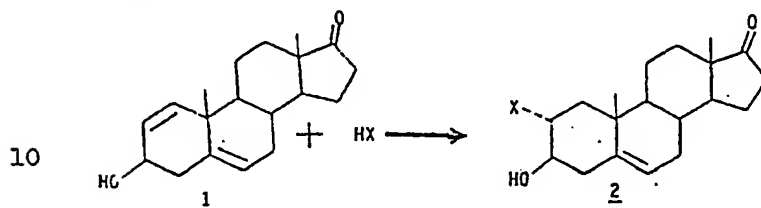
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Selective protection of the Carbon-3 hydroxyl
 in the presence of the 1 α -hydroxyl group should yield 2.
 For example, 1 α ,3 β -dihydroxyandrost-5-en-17-one 1 reacts
 with t-butyl-dimethyl silyl chloride in the presence of
 imidazole using dimethylformamide as a solvent to yield
 1 α ,3 β -dihydroxyandrost-5-en-17-one 3t-butyltrimethylsilyl
 ether, 2. Reaction of 2 with thionyl chloride, or phos-
 phorous tribromide or catechol phosphochloridate followed
 by iodine yields the corresponding 1 β -chloro, bromo or
 iodo derivatives 3. Reaction of 3 (R=Cl, Br, I) with
 tetrabutyl ammonium fluoride yields 1 β -halo-3 β -hydroxy
 androst 5-en-17-one, 4 (R=Cl, Br or I). The fluoride
 (4, R=F) may be synthesized via a similar route using

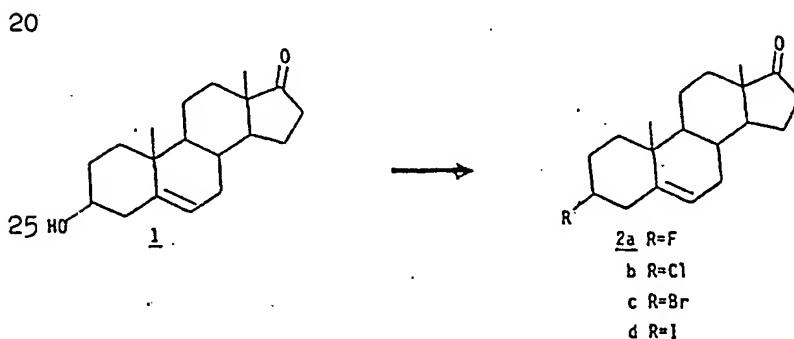
1 an ester as the protecting group at C-3 and reacting the 1 α -hydroxyl group with diethyl (2-chloro-1,1,2-trifluoroethyl)amine. Hydrolysis should yield 1,3-fluoro-3 β -hydroxyandrost-5-en-17-one, 4, R=F.

5 Halogenation at Carbon-2



15 Addition of HX across the C-1 double bond in 3 β -hydroxyandrost-1,5-diene-17-one, 1, yields a mixture of the C-1 and C-2 halogenated steroids. Separation affords 2-halo-3 β -hydroxyandrost-5-en-17-one (2, R=F, Cl, Br, I).

Halogenation at Carbon-3



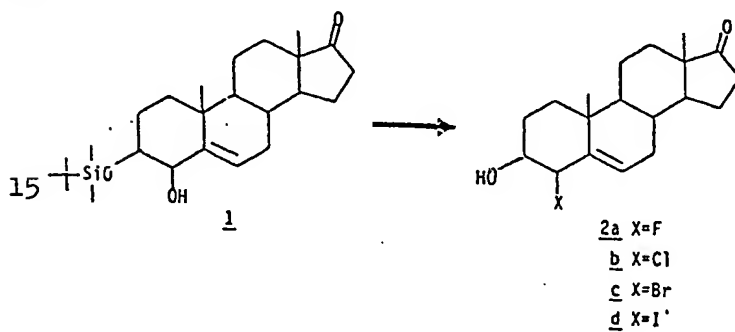
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1 Reaction of 3 β -hydroxyandrost-5-en-17-one 1
 with diethyl (2-chloro-1,1,2-trifluoroethyl) amine
 yields 3 β -fluoroandrost-5-en-17-one 1. Reaction of 1
 with thionyl chloride yields 3 β -chloroandrost-5-en-17-
 5 one, 2b. Reaction of 1 with phosphorus tribromide
 yields 3 β -bromoandrost-5-en-17-one, 2c. Reaction of
1 with catechol phosphochloridate followed by iodine
 yields 3 β -iodoandrost-5-en-17-one 2d.

Halogenation at Carbon-4

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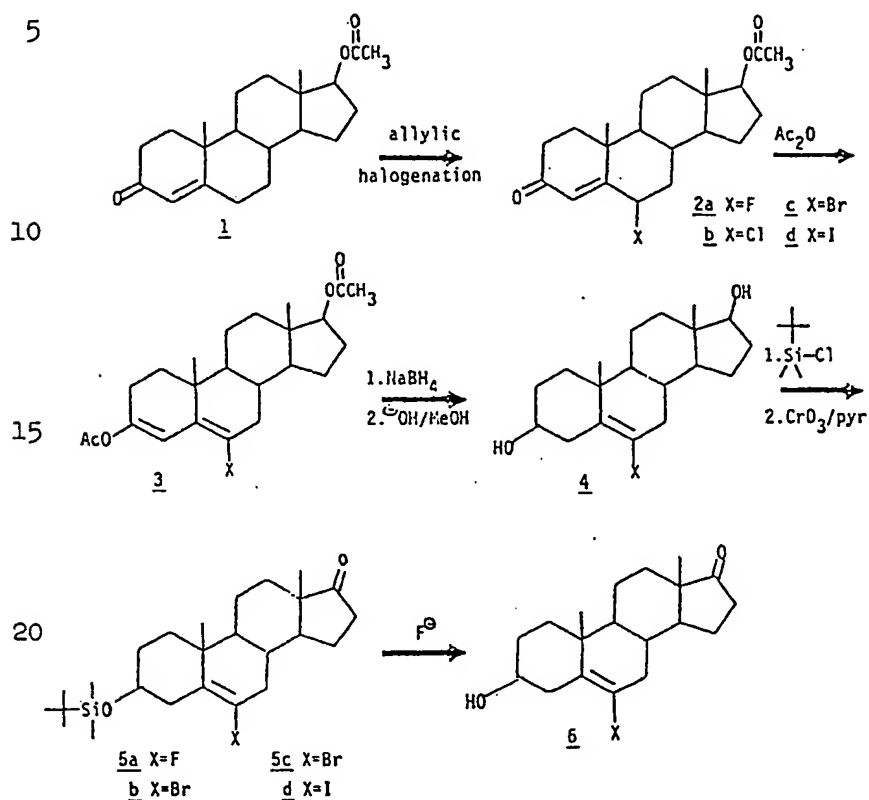
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With the 3 β -hydroxyl group protected as its
 t-butyl-dimethylsilyl ether the C-4 hydroxyl may be
 chlorinated using thionyl chloride. Treatment with
 fluoride ion cleaves the silyl ether to yield 4-chloro-
 25 3 β -hydroxyandrost-5-en-17-one, 2b. Reaction of 3,4-
 dihydroxyandrost-5-en-17-one 3-t-butyldimethylsilyl
 ether 1 with catechol phosphochloridate, followed by
 displacement with bromide ion and cleavage of the silyl
 ether with fluoride ion yields 4-bromo-3 β -hydroxyandrost-
 30 5-en-17-one, 2c. Reaction of 1 with catechol phospho-
 chloridate, followed by iodine and cleavage of the silyl
 ether with fluoride yields 4-iodo-3 β -hydroxyandrost-5-en-
 17-one, 2d. Fluorination of 3,4-dihydroxyandrost-5-en-17-
 one 3-acetate with diethyl (2-chloro-1,1,2-trifluoroethyl)

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1 amine followed by hydrolysis of the ester yields 4-fluoro-3 β -hydroxyandrost-5-en-17-one, 2a.

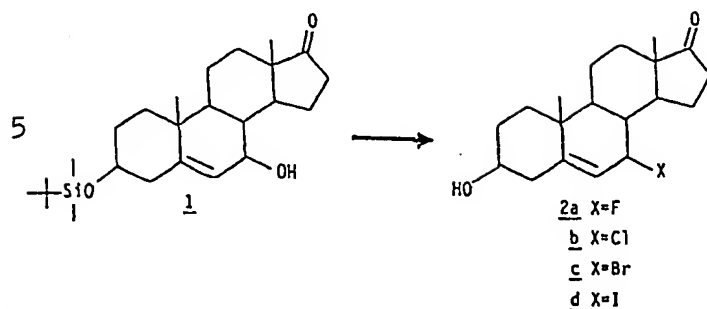
Halogenation at Carbon-6



1 Allylic bromination of 17 β -hydroxyandrost-4-en-3-one 17-acetate 1 using N-bromosuccinimide together with a radical initiator such as light or benzoyl peroxides or aliphatic azo compounds [RR'C(CN)-N=N-C(CN) RR'] e.g. azobisisobutyronitrile yields 6 β -bromo-17 β -hydroxyandrost-4-en-3-one 17-acetate, 2. Allylic chlorination of 1 using sulfuryl chloride together with a radical initiator such as light or benzoyl peroxide or aliphatic azo compounds yields 6 β -chloro-17 β -hydroxyandrost-4-en-3-one 17-acetate, 2c. Allylic iodination of 1 using mercuric iodide and light yields 6 β -iodo-17 β -hydroxyandrost-4-en-3-one-17-acetate, 2d. Acetylation of 2 with acetic anhydride and p-toluene sulfonic acid in toluene yields 6-halo-3,17 β -dihydroxyandrosta-3,5-diene 3,17-diacetate 3. Sodium borohydride reduction of 3 followed by basic hydrolysis of the C-17 acetate yields 6-haloandrost-5-en-3 β ,17 β -diol, 4. Selective protection of the C-3 hydroxyl group as its t-butyldimethylsilyl ether followed by chromium trioxide oxidation of the C-17-hydroxyl group yields 6-halo-3 β -hydroxyandrost-5-en-17-one 3-t-butyldimethylsilyl ether 5. Treatment of 5 with fluoride ion yields 6-halo-3 β -hydroxyandrost-5-en-17-one, 6. The C-6 fluoro analogue may be synthesized from the C-6 bromo diacetate, 3c, by treatment with silver fluoride. Reaction of 6-fluoro-3,17 β -dihydroxyandrosta-3,5-diene-3,17-diacetate, 3a, with sodium borohydride and following the above sequence yields, 6-fluoro-3 β -hydroxyandrost-5-en-17-one, 6a.

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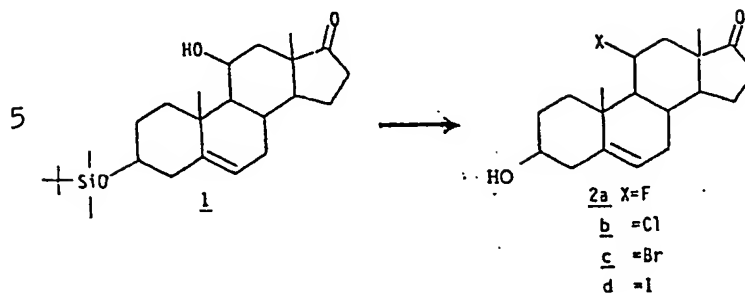
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1 Halogenation at Carbon-7

Reaction of 3β,7-dihydroxyandrost-5-en-17-one-3-t-butyldimethylsilyl ether 1 with thionyl chloride yields the C-7 chloro-steroid. Deprotection of the 3β-hydroxyl group affords 7-chloro-3β-hydroxyandrost-5-en-17-one, 2b. Reaction of 1 with catechol phosphochloridate followed by displacement with bromide ion and deprotection yields 7-bromo-3β-hydroxyandrost-5-en-17-one, 2c. Similarly reaction of 1 with catechol phosphochloridate followed by displacement with iodine and deprotection yields 7-iodo-3β-hydroxyandrost-5-en-17-one, 2d. Fluorination of 3β,7-dihydroxyandrost-5-en-17-one 3-acetate with diethyl (2-chloro-1,1,2-trifluoro-ethyl) amine followed by hydrolysis of the ester yields 7-fluoro-3β-hydroxyandrost-5-en-17-one, 2a.

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1 Halogenation at Carbon-11

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Reaction of 3β,11-dihydroxyandrost-5-en-17-one 3-t-butyldimethylsilyl ether 1 with thionyl chloride yields the C-11 chloro steroid. Deprotection of the 3β-hydroxyl group affords 11-chloro-3β-hydroxyandrost-5-en-17-one, 2b. Reaction of 1 with catechol phosphochloridate followed by displacement with bromide ion and deprotection yields 11-bromo-3β-hydroxyandrost-5-en-17-one, 2c. Similarly reaction of 1 with catechol phosphochloridate followed by displacement with iodine and deprotection yields 11-iodo-3β, hydroxyandrost-5-en-17-one, 2d. Fluorination of 3β,11-dihydroxyandrost-5-en-17-one 3-acetate with diethyl (2-chloro-1,1,2-trifluoroethyl)amine followed by hydrolysis of the ester yields 11-fluoro-3β-hydroxyandrost-5-en-17-one, 2a.

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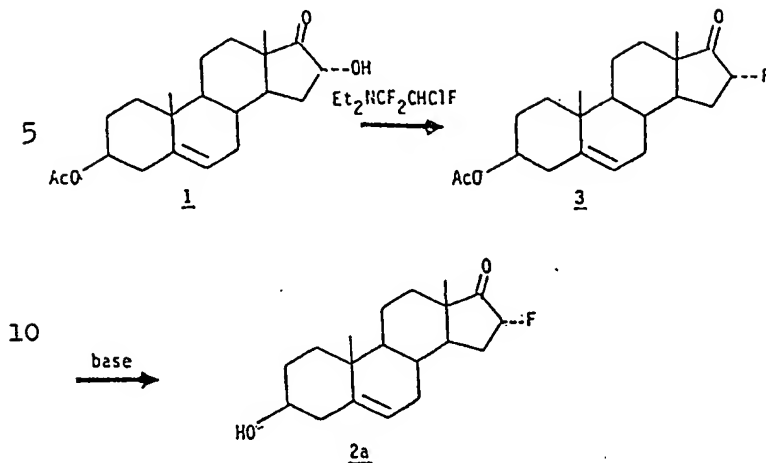
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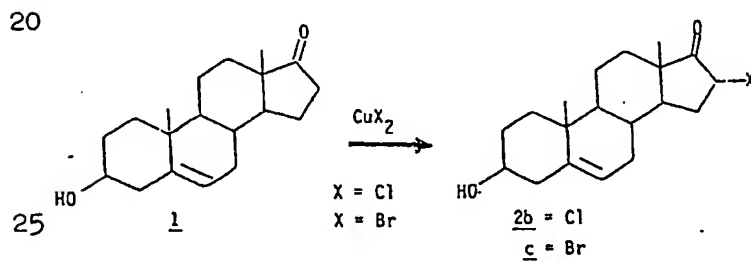
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1 Halogenation at Carbon-16

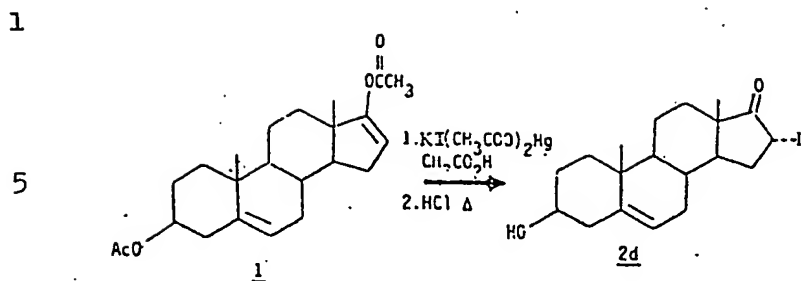


Reaction of 3 β ,16 α -dihydroxyandrost-5-en-17-one 3 β -acetate 1 with diethyl (2-chloro-1,1,2-trifluoroethyl)amine affords 16 α -fluoro-3 β -hydroxyandrost-5-en-17-one 3-acetate 3. Hydrolysis of the ester with base yields 16 α -fluoro-3 β -hydroxyandrost-5-en-17-one, 2a.



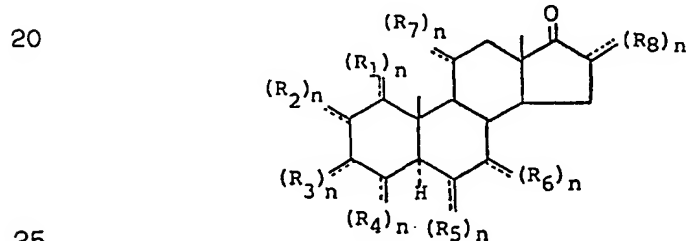
Reaction of 3 β -hydroxyandrost-5-en-17-one 1 with cupric bromide yields 16 α -bromo-3 β -hydroxyandrost-5-en-17-one, 2c¹. Similarly reaction of 1 with cupric chloride yields 16 α -chloro-3 β -hydroxyandrost-5-en-17-one, 2b.

¹E. R. Glazier J. Org. Chem. 1962, 27, 4397



10 Reaction of 3 β ,17-dihydroxyandrosta-5,16-diene
 17-acetate 1 with mercuric acetate followed by treatment
 with potassium iodide yielded the C-17 α iodide which
 hydrolyses with acid to yield 3 β -hydroxy-16 α -iodoandrost-
 5-en-17-one, 2d. Reaction of 2d with silver fluoride
 15 yields 3 β -hydroxy-16 α -fluoroandrost-5-en-17-one, 2a.

The following procedures are illustrative
 for the preparation of compounds of the present inven-
 tion encompassed by the structure:



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and n are as
 defined hereinbefore.

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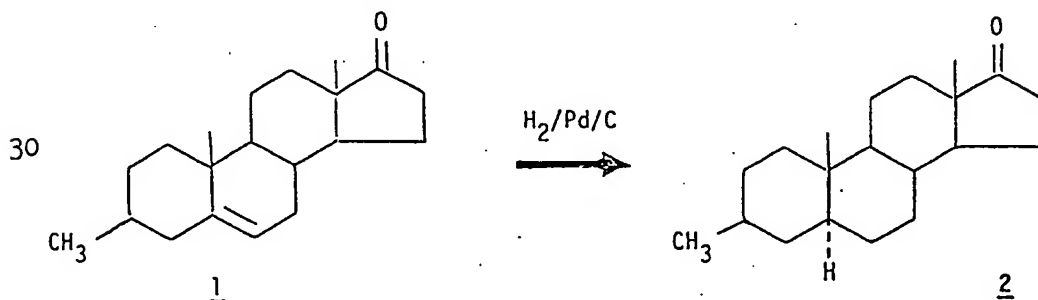
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1 Catalytic hydrogenation of 3 β -substituted androst-5-enes yields almost exclusively 3 β -substituted 5 α -androstanes (for references see J. R. Lewis and C. W. Shoppee, J. Chem. Soc. 1955, 1365). Therefore all the 5 syntheses of the substituted androst-5-enes described above can be used for the synthesis of the substituted 5 α -androstanes, except those molecules which contain reducible double bonds such as the ethenyl and alkynyl derivatives. For these molecules the following syntheses are described.

Firstly an example of catalytic hydrogenation for the synthesis of 5 α -androstanes from androst-5-enes is the synthesis of 3 β -methyl-5 α -androstan-17-one 2 from 3 β -methylandrost-5-en-17-one 1. 3 β -Methylandrost-5-en-17-one 1 (400 mg), prepared as described previously was dissolved in glacial acetic acid (80 ml). Palladium on carbon (10%, 100 mg) was added and the solution maintained under an atmosphere of hydrogen. When hydrogen uptake ceased, the solution was filtered through celite and 20 evaporated to give solid which was recrystallized from methanol to yield 3 β -methyl-5 α -androstan-17-one, 2, (320 mg, 80% yield). MP 107-108°C, ^1H NMR (CDCl_3) δ 0.86 (d, 3H, J-5Hz, methyl at C-3), 0.85 (s, 3H, C-19 Me), 0.79 (s, 3H, C-18 Me).

25 Anal Calc for $\text{C}_{20}\text{H}_{32}\text{O}$: C, 83.26%, H 11.18%

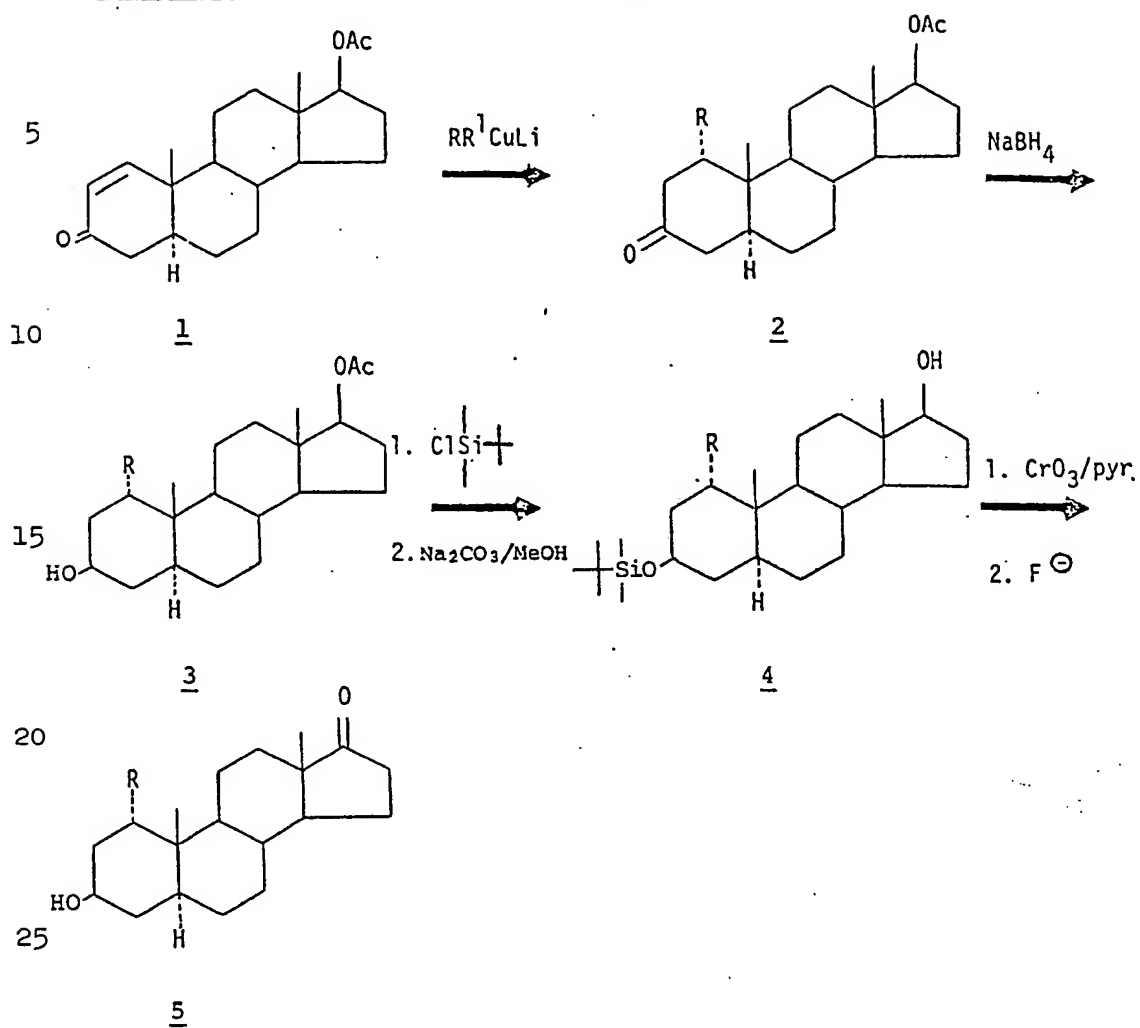
Found: C, 82.99%, H 11.35%



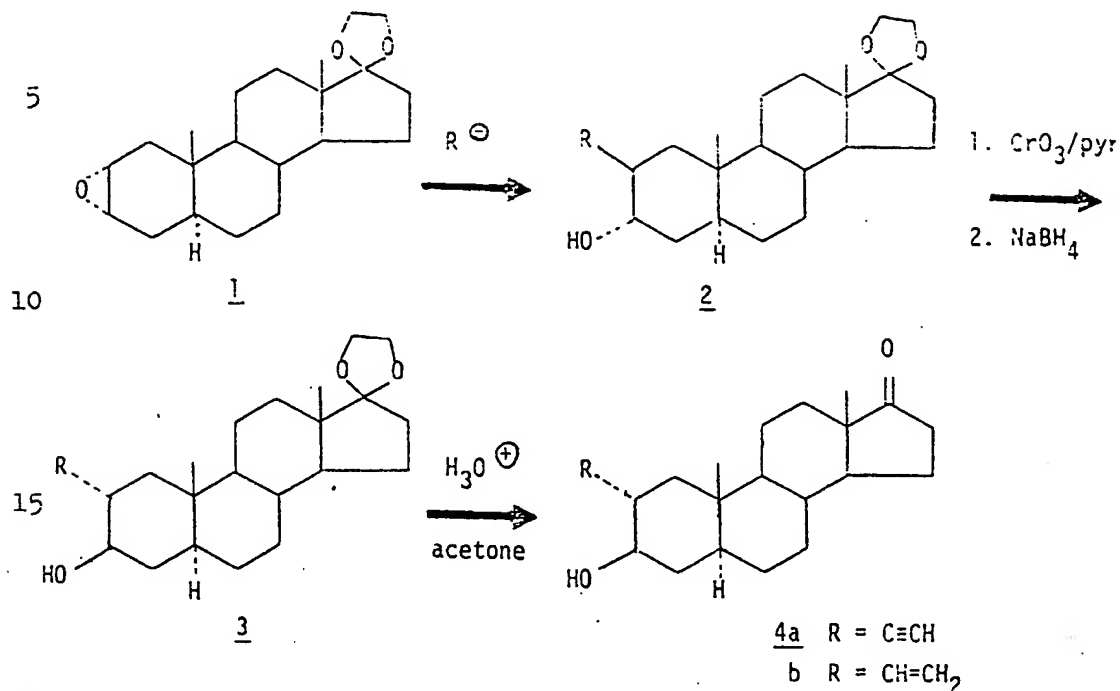
1 The following procedures are illustrative for alkenylation and alkynylation at carbon-1.

Michael addition to 17 β -hydroxy-5 α -androst-1-en-3-one 17-acetate, 1, using a dialkenyl lithium cuprate, 5 (RR¹CuLi, R = R¹ = CH=CHR²) yields the 1 α -alkenyl-17 β -hydroxy-5 α -androstan-3-one 17-acetate 2. Reduction of the C-3 ketone in 2 yields the 3 β -hydroxy steroid 3. Protection of the 3 β -hydroxyl group as a dimethyl-t-butylsilyl ether followed by hydrolysis of the C-17 acetate yields 1 α -10 alkenyl-3 β , 17 β -dihydroxy-5 α -androstan 3-dimethyl-t-butylsilyl ether, 4. Oxidation of the C-17-hydroxyl group and deprotection of the 3 β -hydroxyl group with fluoride ion affords 1 α -alkenyl-3 β -hydroxy-5 α -androstan-17-one, 5. (R = CH=CHR' where R' = alkyl). Alkynylation, to prepare 15 5 (R = C \equiv CR' where R' = alkyl) maybe carried out using the above procedure but with a different organo cuprate reagent. Using 2-tri-n-butylstannyl ethenyl 1'-pentynyl lithium cuprate (R R'CuLi is equivalent to [C₃H₇C \equiv C-Cu-CH=CHSnBu₃]⁻Li⁺), (E. J. Corey and R. H. Wollenberg, 20 J. Amer. Chem. Soc. 1974, 96, 5581), tri-n-butylstannyl-ethylene is added to 1 to yield 2 with R = CH=CHSnBu₃. Oxidation using lead tetraacetate proceeds with loss of tin and affords the corresponding acetylide 2, (R = C \equiv CH). Following through the reaction sequence as above yields 25 1 α -ethynyl-3 β -hydroxy-5 α -androstan-17-one 5, R = C \equiv CH.

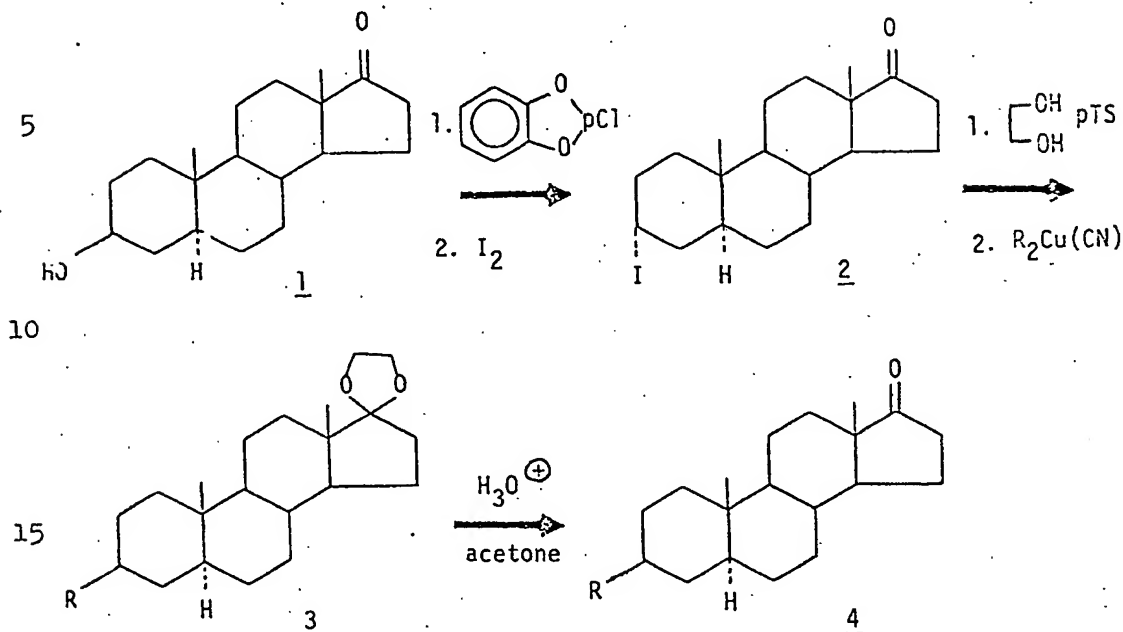
1 Alkenylation and Alkynylation at Carbon-1.



Alkenylation and Alkynylation at Carbon-2.

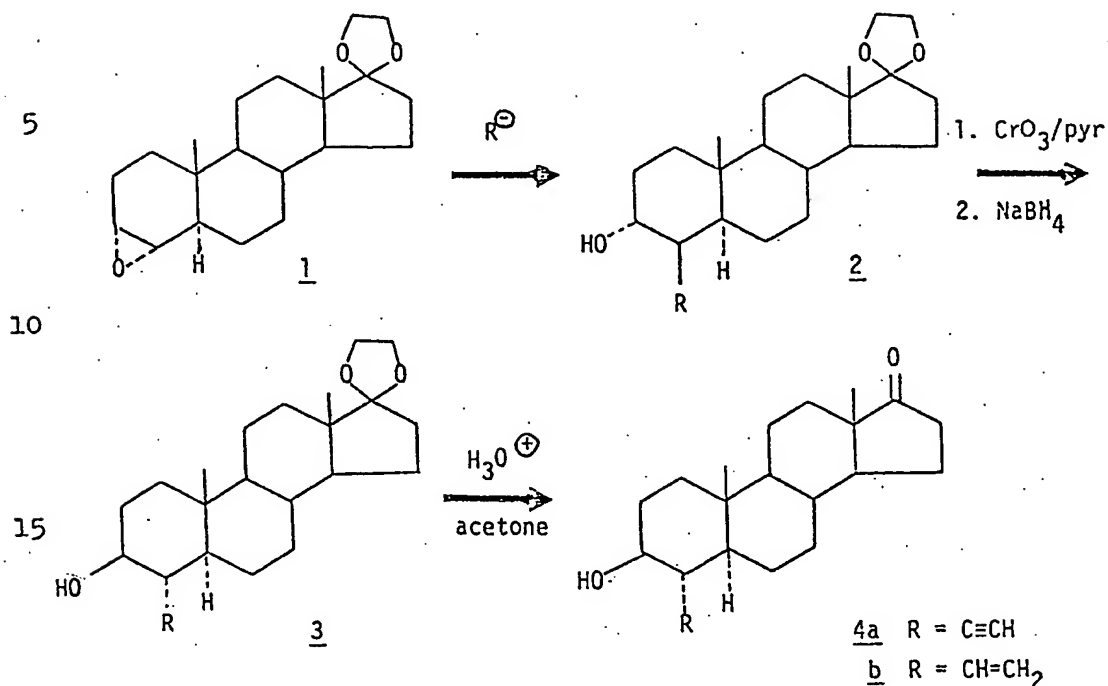


Reaction of 2 α , 3 α -epoxy-5 α -androstan-17-one 17-ketal 1 with lithium acetylide ethylene diamine complex yields 2 β -ethynyl-5 α -androstan-3 α -ol-17-one 17-ketal 2, ($\text{R} = \text{C}\equiv\text{CH}$). Epimerization of the C-3 alcohol by oxidation to the C-3 ketone (chromium trioxide/pyridine) and reduction with sodium borohydride affords 2 β -ethynyl-5 α -androstan-3 β -ol-17-one 17-ketal 3 ($\text{R} = \text{C}\equiv\text{CH}$). Deprotection of the 17-ketone by treatment with aqueous acid yields 2 α -ethynyl-5 α -androstan-3 β -ol-17-one 4a. The 2 α -ethenyl steroid can be synthesized from the ethynyl derivative by careful catalytic reduction with Lindlar catalyst to yield 2 α -ethenyl-3 β -hydroxy-5 α -androstan-17-one, 4b.

1 Alkenylation and Alkynylation at Carbon-3.

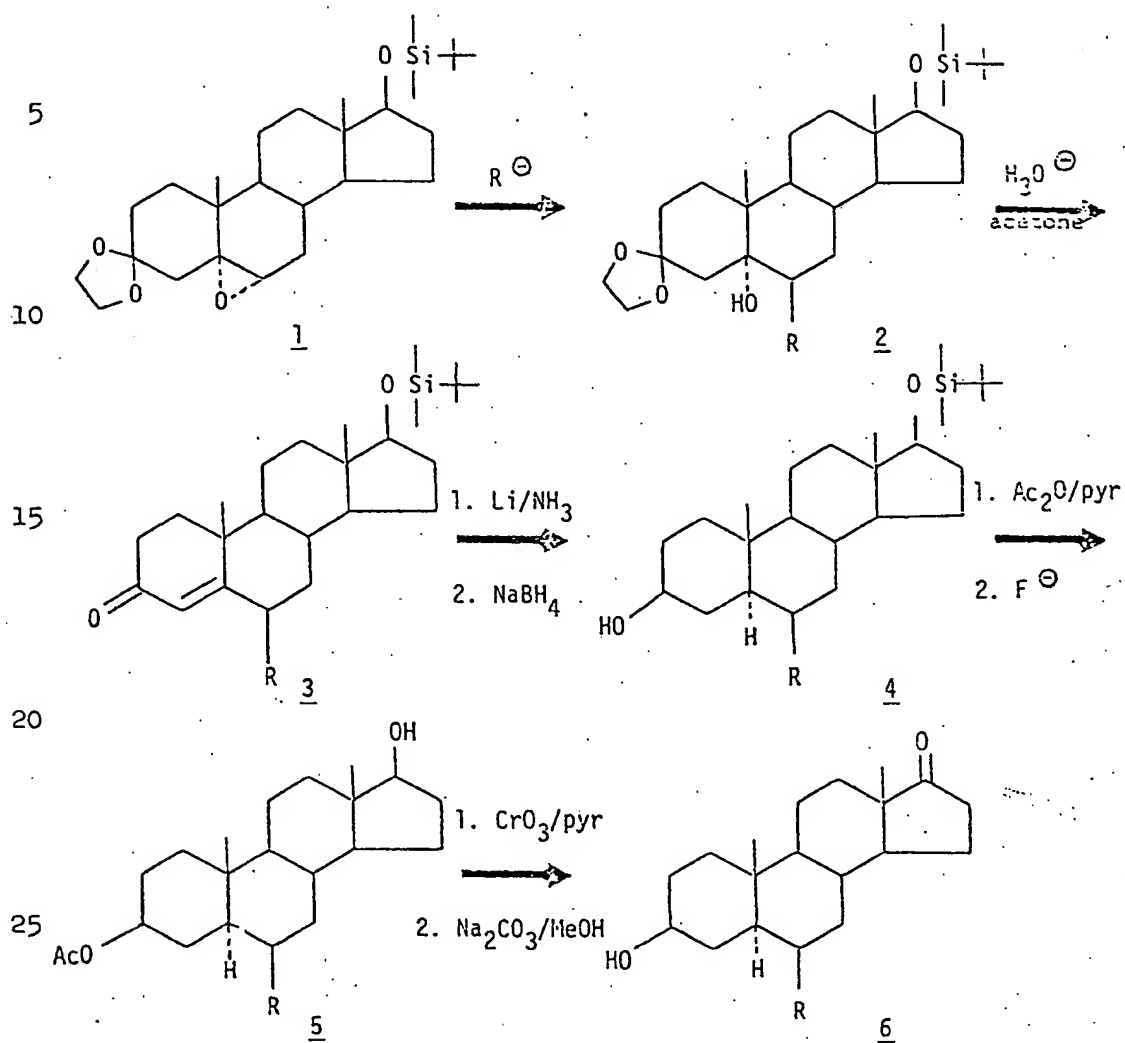
Reaction of 3β-hydroxy-5α-androstan-17-one **1** with catechol phosphochloridate followed by iodine affords 3α-iodo-5α-androstan-17-one, **2**. Protection of the C-17 ketone as a ketal followed by nucleophilic displacement of the C-3α-iodo group yields the 3β-substituted steroid **3**. For alkenylation at C-3, such as introduction of a vinyl group, i.e. **3** ($R = CH=CH_2$), divinyl cyano dilithio cuprate, $[(CH_2=CH)_2 Cu(CN)]Li_2$ is used. Hydrolysis of the C-17 ketal yields 3β-ethenyl-5α-androstan-17-one, **4** ($R = CH=CH_2$). For alkylation 2-tri-n-butylstannyl ethenyl 1'-pentynyl cyano dilithio cuprate, $[C_3H_7C\equiv C-Cu-CH=CHSn-nBu_3(CN)]Li_2$, yields the 3β-ethynyl derivative **3** ($R = C\equiv CH$). Hydrolysis of the C-17 ketal yields 3β-ethynyl-5α-androstan-17-one, **4**, ($R = C\equiv CH$).

1 Alkenylation and Alkynylation at Carbon-4.



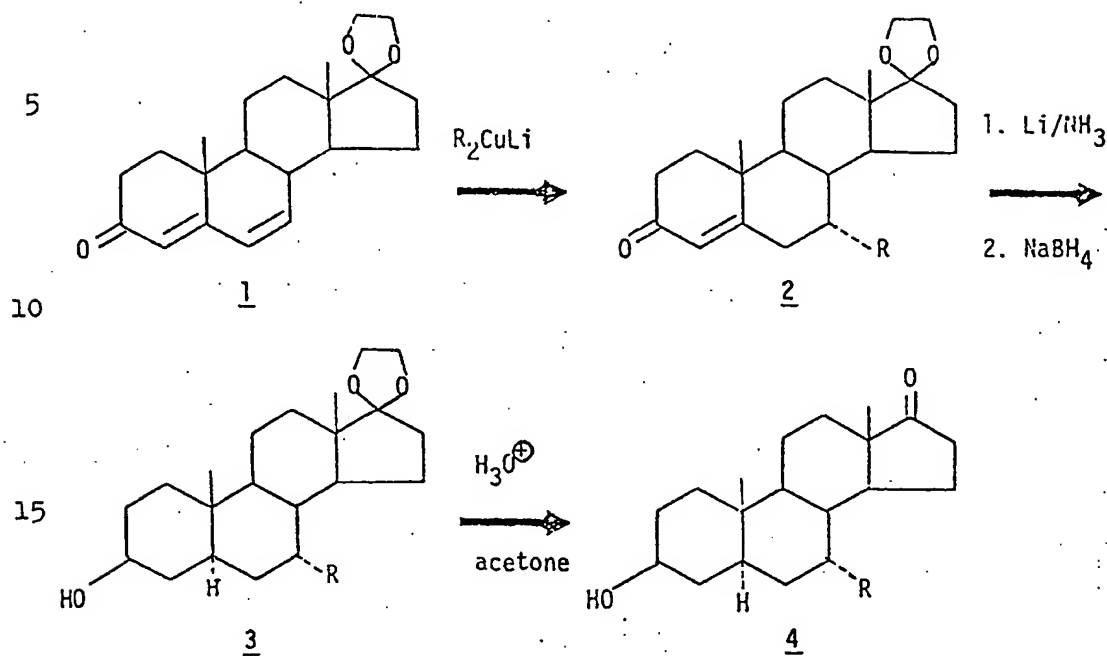
Reaction of 3α,4α-epoxy-5α-androstan-17-one 17-ketal 1 with lithium acetylide diethylamine complex affords 4β-ethynyl-3α-hydroxy-5α-androstan-17-one 17-ketal 2 ($\text{R} = \text{C}\equiv\text{CH}$). Epimerization of the C-3 alcohol by oxidation to the C-3 ketone with chromium trioxide/pyridine followed by reduction with sodium borohydride affords 4α-ethynyl-3β-hydroxy-5α-androstan-17-one 17-ketal 3 ($\text{R} = \text{C}\equiv\text{CH}$). Careful hydrolysis of the C-17 ketal affords 4α-ethynyl-3β-hydroxy-5α-androstan-17-one, 4a ($\text{R} = \text{C}\equiv\text{CH}$). The 4α-ethenyl derivative, 4b, can be synthesized from the ethynyl derivative, 4a, by careful catalytic reduction with Lindlar catalyst or metal ammonia reduction to yield 4α-ethenyl-3β-hydroxy-5α-androstan-17-one, 4b.

1 Alkenylation and Alkynylation at Carbon-6.



- 1 Reaction of 5 α ,6 α -epoxy-3 β -dimethyl-t-butyl-silyl-oxyandrostan-3-one 3-ketal 1, with lithium acetylide-ethylenediamine complex yields 6 β -ethynyl-5 α -hydroxy-3 β -dimethyl-t-butylsilyloxyandrostan-3-one 3-ketal, 2.
- 5 Hydrolysis of the C-3 ketal and dehydration of the consequent β -hydroxy ketone yields the enone 3. If the C-17 silyl group is lost under these hydrolysis conditions the C-17 hydroxyl group will be reprotected. Reduction of
- 10 6 β -ethynyl-17 β -dimethyl-t-butylsilyloxyandrost-4-en-3-one, 3, with excess lithium in ammonia followed by rapid quenching with ammonium chloride affords primarily the 3-keto-4,5 α -dihydro compound. (A. Bowers, H.J. Ringold, and E. Denot, J. Amer. Chem. Soc. 1958, 80, 6115).
- 15 Sodium borohydride reduction of the C-3 ketone yields 6 β -ethynyl-5 α -androstan-3 β ,17 β -diol 17-dimethyl-t-butylsilyl ether, 4. Protection of the C-3 alcohol as an acetate and deprotection at C-17 with fluoride ion yields 6 β -ethynyl-5 α -androstan-3 β ,17 β -diol 3-acetate, 5.
- 20 Oxidation of the C-17 hydroxyl group with chromium trioxide/pyridine followed by deprotection of the C-3-hydroxyl group yields 6 β -ethynyl-5 α -androstan-3 β -ol-17-one, 6. Higher homologues can be synthesized from 6 by first protecting the ketone and alcohol then using
- 25 the acetylide anion to react with primary alkyl halides. The C-6 ethenyl derivatives (6 R= CH=CH₂) can be prepared by reduction of the corresponding C-6 ethynyl derivatives.

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1 Alkenylation and Alkynylation at Carbon-7.

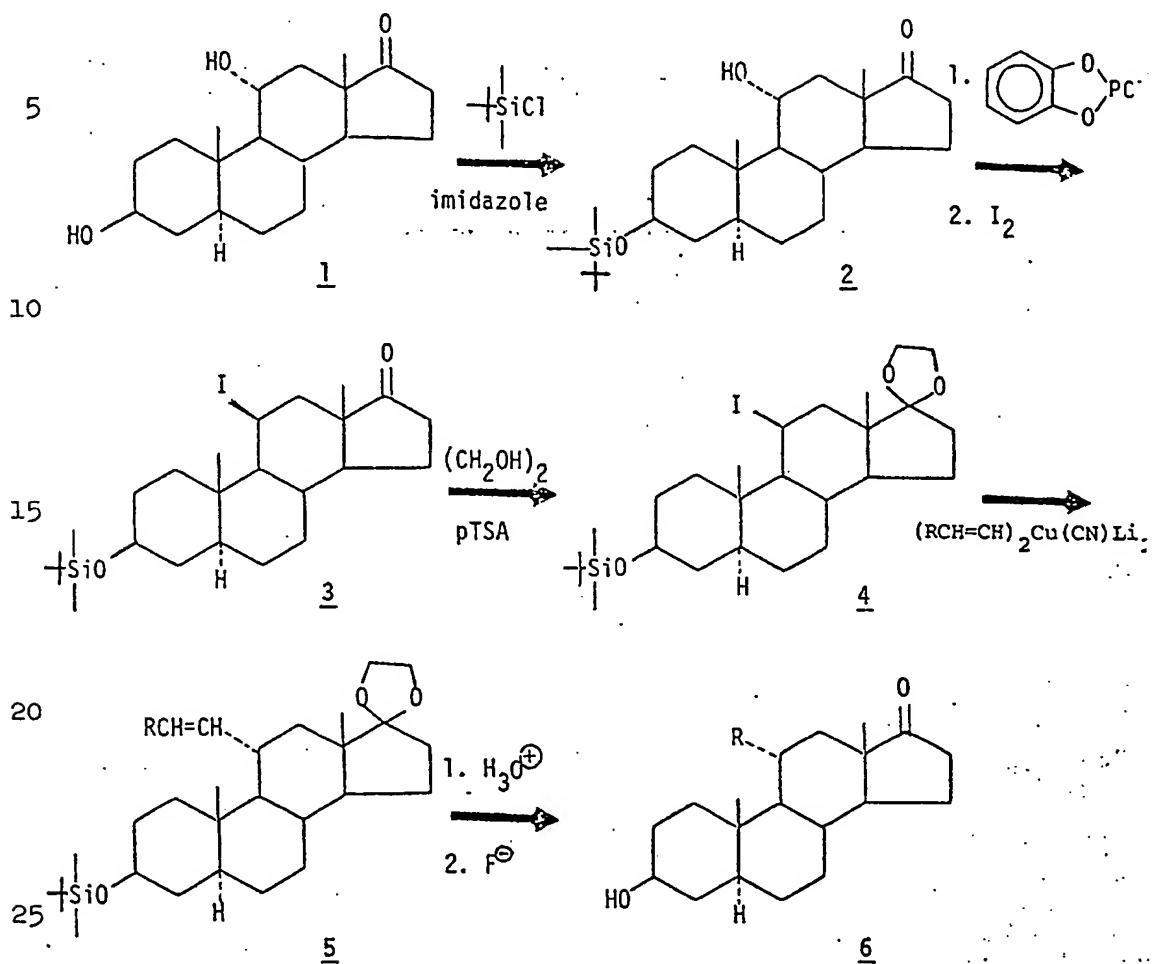
1 Alkenylation of androsta-4,6-dien-3,17-dione
17-ketal 1 with 2-tri-n-butylstannyl ethenyl 1'-pentynyl
lithium cuprate ($[C_3H_7C\equiv C-Cu-CH=CHSn\ nBu_3]Li$) yields the
7 α -alkenyl steroid 2 ($R = CH=CHSn\ nBu_3$). Oxidation using
5 lead tetraacetate proceeds with the loss of tin affords
the corresponding acetylene 2 ($R = C\equiv CH$). Reduction of
7 α -ethynylandrosta-4-en-3,17-dione 17-ketal 2, ($R = C\equiv CH$),
with excess lithium in ammonia followed by rapid quenching
with ammonium chloride affords primarily the 3-keto-4,5 α -
10 dihydro compound. Sodium borohydride reduction of the C-3
ketone yields 7 α -ethynyl-5 α -androstan-3 β -ol-17-one 17-ketal
3. Careful acid hydrolysis of the C-17 ketal yields 7 α -
ethynyl-5 α -androstan-3 β -ol-17-one 4 ($R = C\equiv CH$). Higher
homologues can be synthesized from 4, by first protecting
15 the ketone and alcohol, then using the acetylide anion
to react with primary alkyl halides. The C-7 ethenyl
derivatives 4 ($R = CH=CH_2$) can be prepared by reduction
of the corresponding C-7 ethynyl derivatives.

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1 Alkenylation and Alkynylation at Carbon-11.

1 Reaction of the less hindered 3 β -hydroxy-5 α -androstan-17-one 1 with t-butyldimethylsilyl chloride yields the 3 β -t-butyldimethylsilyl ether 2. Treatment of this first with catechol phosphochloridate followed 5 by displacement with iodine yields 3 β -hydroxy-11 β -iodo-5 α -androstan-17-one 3-dimethyl-t-butylsilyl ether 3. Protection of the C-17 ketone as the 1,3-dioxolane 4 followed by alkenylation using dialkenyl dilithio cyano cuprate, (RCH=CH)₂Cu(CN)Li₂ yields 11 α -alkenyl-3 β -hydroxy- 10 5 α -androstan-17-one-3-t-butyldimethylsilyl ether 5. Deprotection of the C-17 ketone and 3 β alcohol affords 11 α -alkenyl 3 β -hydroxy-5 α -androstan-17-one 6. If 6 has R=2'-tri-n-butylstannyl ethenyl, then lead tetraacetate oxidation affords 11 α -alkynyl-3 β -hydroxy-5 α -androstan-17- 15 one. 6, (R= C \equiv CH).

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Alkenylation and Alkynylation at Carbon-16.

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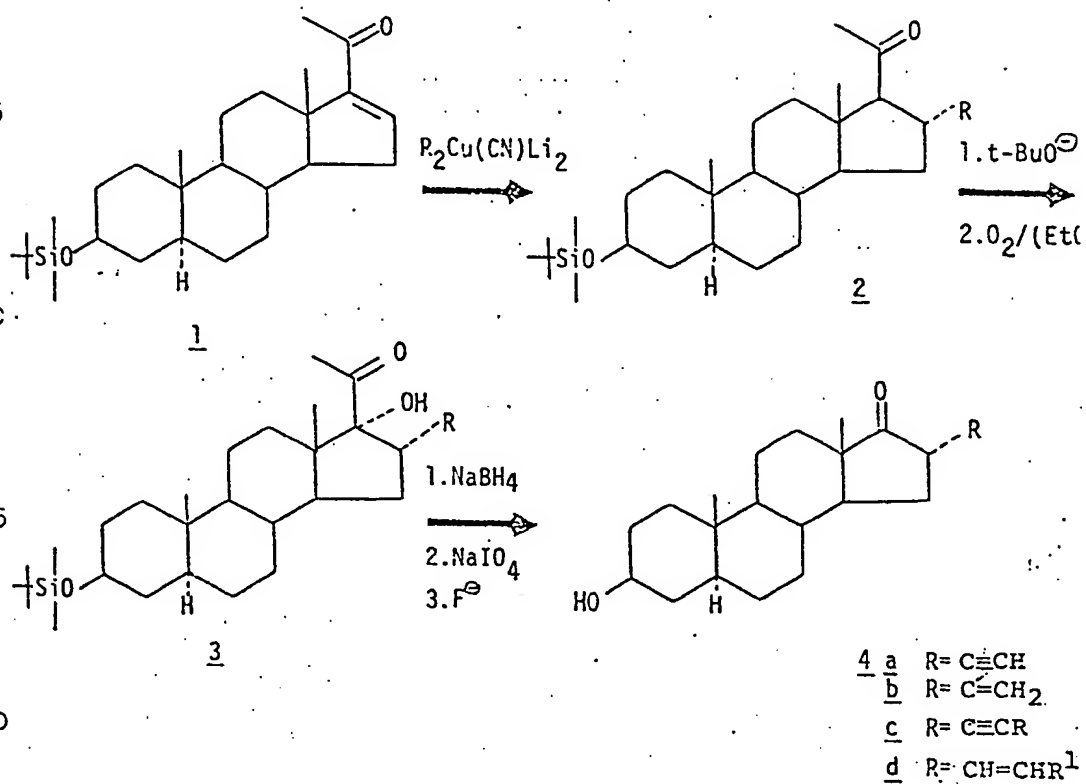
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1 Michael addition of a suitably substituted
organo copper reagent such as 2-tri-n-butylstannyl
ethenyl 1'-pentynyl lithium cuprate ($[\text{C}_3\text{H}_7\text{C}\equiv\text{C}-\text{Cu}=\text{CH}=\text{CH}$
5 $\text{Sn nBu}_3]\text{Li}$) to 3 β -hydroxy-5 α -pregna-16-en-20-one 3-t-
butyl dimethylsilyl ether 1 yields a 16 α -tri-n-butyl-
stannyl ethylene (2, $\text{R} = \text{CH}=\text{CHSn nBu}_3$). Lead tetra-
acetate oxidation proceeds with the loss of tin and
yields the corresponding acetylide. Treatment of 2
with t-butoxide followed by oxygen generates a C-16 α -
10 hydroperoxide which is reduced by triethylphosphite
to 16 α -ethynyl-3 β ,17 α -dihydroxy-5 α -pregnan-20-one 3-t-
butyldimethylsilyl ether 3. Reduction of the C-20
ketone to an alcohol followed by cleavage of the diol
with sodium periodate and deprotection of the 3 β -hydroxyl
15 group with fluoride, yields 16 α -ethynyl-3 β -hydroxy-5 α -
androstan-17-one, 4a ($\text{R} = \text{C}\equiv\text{CH}$). Careful reduction of
the acetylene in 4a should afford the 16 α -vinyl sub-
stituted steroids, 4b ($\text{R} = \text{CH}=\text{CH}_2$). Higher homologues
of these substituents may be synthesized via acetylide
20 chemistry using 4a with its hydroxyl and ketone groups
first protected. Reduction of the substituted acetylene
will afford both E and Z olefinic substituents at C-16.

In order to determine the pharmacological
activity of the novel and other-steroids of the present
25 invention, the following experiments are carried out.

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Inhibition of G6PDH

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The compounds are screened as inhibitors of purified bovine adrenal G6PDH activity as one predictor of cancer preventive action. The results are shown in Table I:

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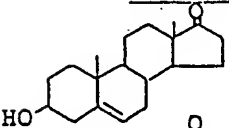
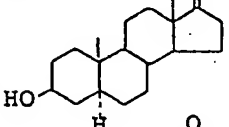
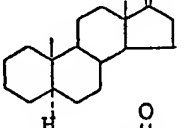
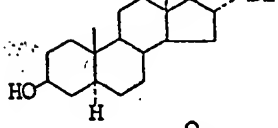
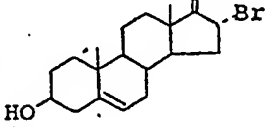
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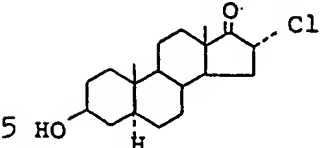
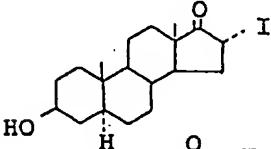
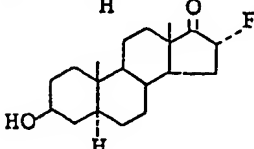
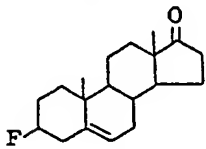
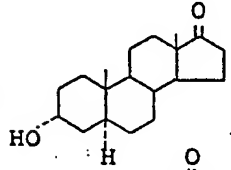
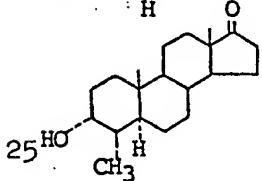
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<u>Compound</u>	<u>No.</u>	<u>Conc.</u>	<u>Per Cent Inhibition</u>
	<u>1</u>	10 μ m	53
		1 μ m	36
		0.1 μ m	12
	<u>2</u>	10 μ m	82
		1 μ m	64
		0.1 μ m	36
	<u>3</u>	10 μ m	80
		1 μ m	69
		0.1 μ m	10
	<u>4</u>	10 μ m	90
	<u>5</u>	10 μ m	74

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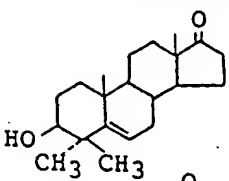
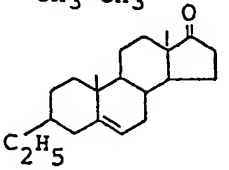
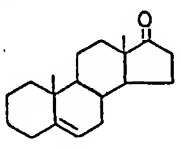
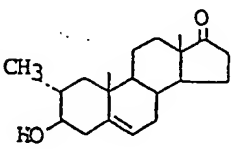
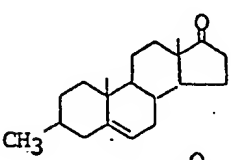
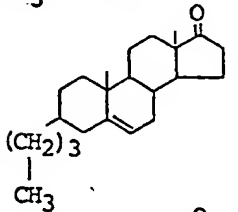
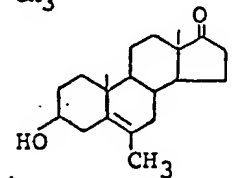
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1	Compound	No.	Conc.	Per Cent Inhibition
5		<u>6</u>	10 μ m	72
10		<u>7</u>	10 μ m	51
15		<u>8</u>	10 μ m	66
20		<u>9</u>	10 μ m	22
25		<u>10</u>	10 μ m	35
30		<u>11</u>	10 μ m	35

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1	Compound	No.	Conc.	Per Cent Inhibition
5		<u>12</u>	10 μm	48
10		<u>13</u>	10 μm 1 μm 0.1 μm	73 55 58
15		<u>14</u>	10 μm 1 μm 0.1 μm	60 15 0
20		<u>15</u>	10 μm 1 μm 0.1 μm	46 40 26
25		<u>16</u>	10 μm 1 μm 0.1 μm	53 40 25
30		<u>17</u>	10 μm 1 μm 0.1 μm	60 45 49
35		<u>18</u>	10 μm 1 μm 0.1 μm	45 18 10

1 Inhibition of TPA (Tumor Promoter) Stimulation
 of Mouse Epidermal DNA

Synthesis rate by orally administered steroids.

5 The inhibition of tumor promoter stimulation of
mouse epidermal DNA synthesis rate by steroids may also
contribute to cancer preventive activity. The following
assay is used:

10 ICR male mice (7-9 weeks old) were shaved on
the back 1-2 days before use. Only mice showing no hair
regrowth were used. Animals were orally intubated with
a particular steroid suspended by homogenization in
sesame oil or with sesame oil alone (controls). One
hour later TPA (10 µg in 0.2 ml of acetone) or acetone
15 vehicle was applied topically to the shaved skin. Twenty
hours later, mice were injected i.p. with 60 µCi of ³H-
thymidine 20 minutes before sacrifice. The animals were
killed by cervical dislocation and the residual hair
was removed with a depilatory agent. Epidermal scrapings
were prepared according to the procedures of Hennings
20 et al. (Cancer Res. 28, 53, 1968), homogenized in dis-
tilled water at 4°C, and the macromolecules precipitated
with 0.4 N trichloroacetic acid (TCA). Following 6
washes with absolute ethanol at room temperature, the
nucleic acids were hydrolyzed with 0.5 N TCA at 70°C for
25 5 minutes. The hydrolysate (0.2 ml aliquots) were counted
in an Intertechnique scintillation counter and assayed
for DNA by the diphenylamine reaction.

30 The data are expressed as counts per minute
(cpm) of tritium per µg of DNA.

	<u>cpm/ug DNA</u>
1 Control (no TPA and no steroid)	37 \pm 6.1 (number (n) of animals = 3)
TPA	101 \pm 20
TPA + DHEA (compound 1)* (400 mg/kg)	42 \pm 7
5 TPA + DHEA (200 mg/kg)	88 \pm 9.3
TPA + DHEA (100 mg/kg)	87 \pm 8.2
TPA + Compound <u>2</u> * (200 mg/kg)	100 \pm 6.0
TPA + Compound 2* (100 mg/kg)	97 \pm 15
TPA + Compound <u>3</u> * (200 mg/kg)	64 \pm 10
10 TPA + Compound <u>3</u> * (100 mg/kg)	113 \pm 21

* of Table 1

Conclusion: DHEA is active at blocking the TPA stimulation in DNA synthesis rate at 400 mg/kg but not at 200 mg/kg or 100 mg/kg. Compound 2 is not active at 200 mg/kg or 100 mg/kg. Other tests in which compound 2 or compound 3 and DHEA were given by i.p. injection in a dose-response experiment indicated that 2 is about as active as DHEA and compound 3 was more active in blocking the TPA stimulation in DNA synthesis rate.

Compound 3 appears somewhat more active than DHEA at the dose of 200 mg/kg administered orally.

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1 Compound 2 or 3 in comparison with DHEA by Intraperi-
toneal Injection.

5 Steroids were suspended in sterile 95% saline -
 5% Emulphor and injected intraperitoneally. Otherwise
 conditions were the same as when steroids were orally
 administered.

	<u>Compound 2 vs. DHEA</u>	<u>cpm/μg DNA</u>
10	Control (no steroid or TPA)	63 ± 3.9 (n = 2)
	TPA	170 ± 2.2
	DHEA (10 mg/kg i.p.) + TPA	66 ± 2.1
	DHEA (2 mg/kg i.p.) + TPA	105 ± 12
	DHEA (0.4 mg/kg i.p.) + TPA	157 ± 4.2
15	Cpd <u>2</u> (10 mg/kg i.p.) + TPA	58 ± 0.9
	Cpd <u>2</u> (2 mg/kg i.p.) + TPA	94 ± 1.8
	Cpd <u>2</u> (0.4 mg/kg i.p.) + TPA	148 ± 3.0

	<u>Compound 3 vs. DHEA</u>	<u>cpm/μg DNA</u>
20	Control (no steroid or TPA)	46 ± 5.3
	TPA	114 ± 37
	Cpd <u>3</u> (10 mg/kg i.p.) + TPA	8.9 ± 3.0
	Cpd <u>3</u> (2 mg/kg i.p.) + TPA	27 ± 8.8
	Cpd <u>3</u> (0.4 mg/kg i.p.) + TPA	32 ± 2.4

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1 Compound 16* vs. DHEA

A similar oral dose-response experiment with compound 16 and DHEA was performed.

5		<u>cpm/μg DNA</u>
	Control (no TPA, no steroid)	55 \pm 3.7 (n=2)
	TPA	162 \pm 2.1
	TPA + DHEA (400 mg/kg)	50 \pm 2.8
	TPA + DHEA (200 mg/kg)	155 \pm 1.6
10	TPA + DHEA (100 mg/kg)	169 \pm 11
	TPA + Compound 16* (400 mg/kg)	39 \pm 1.1
	TPA + Compound 16* (200 mg/kg)	44 \pm 2.5
	TPA + Compound 16* (100 mg/kg)	100 \pm 19

15

*of Table I

Conclusion: Compound 16 is about 3X as active as DHEA in this test.

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1 Anti-Obesity Test

Male A/J mice (5 weeks old) were obtained from the Jackson Laboratory and were housed in polycarbonate cages (5 mice/cage) in animal quarters maintained at $24 \pm 1^\circ\text{C}$ with 12 hours of light and 12 hours of darkness each day. One week after arrival, the mice were placed on a chow diet containing varying concentrations of DHEA or other steroid. Animals were weighed weekly; food consumption was determined weekly by subtracting the amount of food remaining in the cage from the amount added.

Compound 3 vs. DHEA

15	Week	Control (no steroid)	DHEA 0.7% mean weekly weight in grams(n=5)	Cpd 3 0.35% mean weekly weight in grams(n=5)	Cpd 3 0.7%
	0	21.6 \pm 2.6	21.1 \pm 2.8	21.8 \pm 2.2	21.6 \pm 2.6
	1	22.6 \pm 2.1	15.2 \pm 1.8	22.6 \pm 1.8	20.0 \pm 1.9
	2	23.4 \pm 1.8	17.0 \pm 2.0	23.6 \pm 1.8	21.3 \pm 1.8
20	3	24.6 \pm 2.3	17.8 \pm 1.1	24.8 \pm 1.8	21.8 \pm 1.6
	4	25.4 \pm 2.5	18.8 \pm 1.1	24.6 \pm 1.8	22.0 \pm 1.6
	5	26.0 \pm 2.3	18.2 \pm 1.3	24.8 \pm 1.9	21.4 \pm 1.4

There was an initial depression in food consumption in the DHEA treated mice in the first week. Thereafter the food consumption was equal to or slightly greater than the control mice.

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1 Compound 2 vs. DHEA

Week	Control	DHEA 0.35%	DHEA 0.7%	Cpd 2 0.35%	Cpd 2 0.7%	
		mean weekly weight in grams (n=5)				
5	0	21.6 ± 1.3	21.8 ± 2.2	22.0 ± 2.5	21.8 ± 1.6	21.3 ± 1.8
	1	21.4 ± 2.1	20.0 ± 2.3	17.0 ± 1.9	21.8 ± 1.3	20.6 ± 2.3
	2	22.0 ± 0.7	19.2 ± 1.8	17.8 ± 1.8	22.0 ± 1.2	20.6 ± 0.5
	3	22.2 ± 0.8	19.6 ± 2.8	18.4 ± 1.8	22.8 ± 1.3	20.8 ± 0.8
	4	24.0 ± 1.0	22.2 ± 2.4	19.2 ± 1.6	24.2 ± 1.1	22.6 ± 0.6
10	5	24.8 ± 0.8	21.8 ± 2.2	20.2 ± 1.9	24.4 ± 1.7	22.4 ± 0.5
	6	25.2 ± 1.1	22.8 ± 2.3	19.8 ± 2.0	24.8 ± 1.5	23.5 ± 0.9
	7	25.6 ± 1.1	23.2 ± 2.4	20.6 ± 2.2	25.4 ± 1.7	23.8 ± 0.8

15 Compound 16 vs. DHEA

			DHEA 0.18%	DHEA 0.35%	Cpd 16 0.18%	
Week	Control		mean weekly	weight in	grams (n=5)	Cpd 16 0.35%
20	0	21.6 ± 2.8	22.4 ± 1.8	22.4 ± 2.3	22.6 ± 2.7	22.0 ± 2.5
	1	23.0 ± 1.6	20.4 ± 1.9	16.0 ± 1.6	19.8 ± 2.3	16.8 ± 1.6
	2	24.4 ± 1.6	21.1 ± 0.5	20.2 ± 0.9	19.4 ± 2.1	18.2 ± 0.8
	3	25.6 ± 1.9	22.4 ± 0.8	21.0 ± 0.8	19.4 ± 2.1	17.2 ± 1.7
	4	26.6 ± 1.5	23.6 ± 1.5	22.2 ± 0.9	19.6 ± 2.2	17.0 ± 1.2

25 Compound 16 is more than 2X as active as DHEA in
this test.

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1 Anti-Hyperglycemic Activity

Coleman et al. (Diabetes 31, 830, 1982) reported that administration of DHEA (0.4% of the diet) produced a marked hypoglycemic effect in C57BL/KsJ-db/db mice and significantly prolonged their lifespan. The authors noted that "diabetes is more severe and develops more rapidly in males and can be improved or circumvented by combined estradiol and progesterone treatment" and suggested that the therapeutic effect of DHEA might result from its metabolism to estrogens. Compound 16 (which has been found herein to be devoid of estrogenic activity in the rat uterotrophic test) was tested in this model.

C57BL/KsJ-db/db 8 week old female mice were obtained and housed in polycarbonate cages in animal quarters maintained at 24°C with 12 h of light and 12 h of darkness each day.

Mice were placed on a control chow or a chow diet containing either 0.4% DHEA or 0.2% of compound 16.

For determination of blood glucose levels, mice were bled from the orbital sinus using a heparinized capillary tube. 0.2 ml of blood was added to 1.8 ml of water to hemolyze the blood and glucose concentration was determined using the glucose oxidase assay.

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Blood Glucose Levels (mg/deciliter)

<u>Week</u>	<u>Control (n=6)</u>	<u>DHEA (0.4%) (n=6)</u>	<u>Cpd. 16 (0.2%) (n=6)</u>
5			
0	232 \pm 43	232 \pm 28	244 \pm 32
1	336 \pm 37	132 \pm 14	143 \pm 21
2	394 \pm 20	135 \pm 37	134 \pm 13

All mice placed
on control diet.

10

24 hrs.	399 \pm 15	192 \pm 32	147 \pm 10
48 hrs.	397 \pm 13	310 \pm 37	262 \pm 23

When mice were taken off diets containing DHEA
or compound 16 and placed on control diet, blood glucose
levels increased at 24 and 48 hrs. but significantly more
slowly in the mice that had received compound 16.

Anti-Autoimmune Activity

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New Zealand Black (NZB) mice develop a pro-
gressive autoimmune, Coomb's positive hemolytic anemia
with age. It has been previously found that long-term
treatment of NZB mice with DHEA significantly inhibits
the rate of development of the autoimmune anemia. In
other studies reported herein, we have determined that
certain steroids, such as compound 16, have retained
the anti-obesity, cancer preventive, and anti-hyper-
glycemic action of DHEA without any apparent estrogenic
effect. There is a reasonable probability that such
steroids will also retain the anti-autoimmune activity
of DHEA.

30

1 The following are additional data on the anti-hyperglycemic effect of compound 16 vs. DHEA.

5

<u>Blood Glucose Levels (mg/deciliter)</u>			
<u>Week</u>	<u>Control (n=7)</u>	<u>DHEA (0.4%) (n=7)</u>	<u>Cpd 16 (0.2%) (n=7)</u>
0	213 ± 54	214 ± 59	216 ± 61
1	292 ± 29	161 ± 19	135 ± 15
2	335 ± 20	145 ± 19	118 ± 12
10 3	354 ± 27	117 ± 12	102 ± 8
4	387 ± 15	112 ± 4	105 ± 5

Compound 16 is more effective in lowering blood glucose concentration at an administered dose of 0.2% in 15 the diet than is DHEA at a dose of 0.4%.

Anti-Hypercholesterolemic Activity

20 Six-week old female ICR mice were obtained and placed in animal quarters at 24°C with 5 animals/cage with food and water ad libitum. All mice (except the control group) received 0.1% PTU (propylthiouracil) in their drinking water. Mice receiving DHEA or compound 4 were injected with the steroid i.p. (15 mg/kg) 3X weekly.

25 For serum cholesterol determinations, mice were bled from the orbital sinus. Blood was allowed to coagulate and was centrifuged to obtain serum. Cholesterol was measured according to the procedure of Rao et al. (Lipids 12, 1078, 1977).

30

35

1 <u>Experimental Group</u>	<u>No. Mice</u>	<u>Serum Cholesterol (mg%)</u>		
		<u>before treatment</u>	<u>1 wk</u> <u>after treatment</u>	<u>2 wk</u> <u>after treatment</u>
5 Control (no steroid or PTU)	30	53.8 \pm 9.3	54.0 \pm 4.0	59.2 \pm 7.2
PTU	40	51.3 \pm 6.1	75.6 \pm 12.9	76.6 \pm 2.4
PTU + DHEA	10	61.0 \pm 6.8	57.3 \pm 3.6	57.5 \pm 3.2
PTU + Cpd 4	10	58.1 \pm 5.6	53.4 \pm 5.2	—

10

Uterotrophic Test for Estrogenic Activity. Compound
16 vs. DHEA and Estradiol-benzoate. Compounds Given by
Oral Administration.

- 15 Twenty-two day old rats were obtained from Charles River Laboratories. Animals were used at 29 days of age. Test steroids were suspended by homogenization in sesame oil. Rats were orally intubated at 1-2 P.M. for 3 days with a test steroid in sesame oil or with sesame oil alone (control).
 20 On the 4th day the animals were killed and the uteri were removed and weighed.

	<u>Mean Uterine Weight (Mgs) (n=6)</u>
Control (no steroid)	166 \pm 34
25 DHEA (400 mg/kg)	261 \pm 23 (p<0.001, greater than control)
Compound 16 (400 mg/kg)	174 \pm 20
Compound 16 (200 mg/kg)	189 \pm 14
Estradiol-benzoate (14 μ g/kg)	244 \pm 44 (p<0.01)

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1 Compound 2 vs. DHEA. Compounds Administered by Subcu-
taneous Injection

5 Steroids were dissolved in 2 ml ethanol and brought up to 5 ml volume with propylene glycol. Concentrations were such that 1 μ l/gm body weight delivered the indicated dose.

Mean Uterine Weight (Mgs) (n=4 or 5)

10 Control (no steroid)	152 \pm 22
DHEA (60 mg/kg) p < 0.02	290 \pm 72
DHEA (10 mg/kg)	152 \pm 17
Compound <u>2</u> (60 mg/kg)	127 \pm 32
Compound <u>2</u> (10 mg/kg)	151 \pm 32

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The above test is being repeated at the oral dose of 400 mg/kg, which would have been more appropriate, since this is a therapeutic dose.

Conclusion: Neither compounds 16 nor 2 are estrogenic at 20 doses at which DHEA is significantly estrogenic.

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1 Summary

Compound 16 is without estrogenic activity in the uterotrophic test and is approximately 3X as active as DHEA in the mouse skin tumor promoter assay and in
5 the anti-obesity test. Compound 2 is without estrogenic activity but is about 1/3 as active as compound 16 in the skin tumor promoter test and only 1/6 as active in the anti-obesity test. However, compound 3 is only about 1/2 as active as compound 16 in the skin tumor
10 promoter test and 1/6 as active in the anti-obesity test.

Compound 15 is about as active as DHEA and compound 16 in the G6PDH inhibition test.

The compounds, i.e. therapeutic agents of this
15 invention may be administered alone or in combination with pharmaceutically-acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may
20 be administered orally in the form of tablets, pills or capsules containing such excipients as starch, milk sugar, certain types of clay and so forth. They may be administered orally in the form of solutions which may contain coloring and flavoring agents or they may be injected
25 parenterally, that is, intramuscularly, intravenously or subcutaneously. For parenteral administration, they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

30 The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the

1 particular compound chosen, and furthermore, it will vary
with the particular patient under treatment. He will
generally wish to initiate treatment with small dosages
substantially less than the optimum dose of the compound
5 and increase the dosage by small increments until the
optimum effect under the circumstances is reached. It
will generally be found that when the composition is
administered orally, larger quantities of the active
agent will be required to produce the same effect as
10 a smaller quantity given parenterally. The compounds
are useful in the same manner as comparable therapeutic
agents and the dosage level is of the same order of
magnitude as is generally employed with these other
therapeutic agents.

15 When given orally, the therapeutic doses of
the compounds of the present invention are generally
in the range of from about 4 to about 450 mg/kg/day
depending upon the particular mammalian host and the
particular effect desired, e.g. cancer preventive, anti-
20 obesity, anti-diabetes, etc., when given by parenterally,
the compounds are administered generally in dosages of,
for example, 0.5 to about 15 mg/kg/day also depending
upon the host and effect desired.

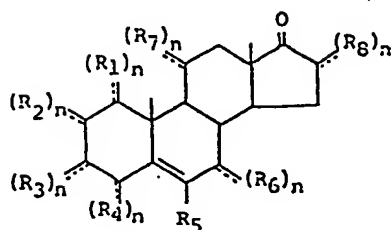
Obviously, other modifications and variations
25 of the present invention are possible in the light of
the above teachings. It is, therefore, to be understood
that changes may be made in the particular embodiments
of this invention which are within the full intended scope
of the invention as defined by the appended claims.

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CLAIMS

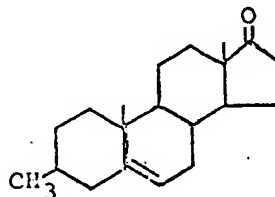
1. A compound of the formula



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are each
 10 independently selected from the group consisting of
 hydrogen, alkyl, alkenyl, alkynyl, halogen and hydroxyl,
 n is an integer from 1 to 2 inclusive with the proviso
 that when R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 or R_8 is alkenyl
 or alkynyl, n is 1; and with the further provisos that
 15 when R_3 is hydroxy, any one of the substituents R_1 , R_2 ,
 R_4 , R_5 , R_6 , R_7 or R_8 is other than hydrogen; when R_3 is
 hydroxy, R_1 may only be alkyl when any one of R_2 , R_4 , R_5 ,
 R_6 , R_7 or R_8 is other than hydrogen; when R_3 is hydroxy,
 R_2 may only be alkyl when any one of R_1 , R_4 , R_5 , R_6 , R_7
 20 or R_8 is other than hydrogen; when R_3 is hydroxy, R_4 may
 only be halogen when R_1 , R_2 , R_5 , R_6 , R_7 or R_8 is other
 than hydrogen; when R_3 is hydroxy, R_6 may only be hydroxy
 or methyl when R_1 , R_2 , R_4 , R_5 , R_7 or R_8 is other than
 hydrogen; when R_3 is hydroxy, R_7 may only be hydroxy when
 25 R_1 , R_2 , R_4 , R_5 , R_6 or R_8 is other than hydrogen; and when
 R_3 is hydroxy, R_8 may only be methyl, ethyl, hydroxy or
 halogen when R_1 , R_2 , R_4 , R_5 , R_6 or R_7 is other than
 hydrogen; and when R_3 is hydroxy, R_5 may be alkyl only
 when R_1 , R_2 , R_4 , R_6 , R_7 or R_8 are other than hydrogen.

- 1 2. The compound as in Claim 1 wherein said alkyl
is lower alkyl containing from 1 to 5 carbon atoms.
3. The compound as in Claim 1 wherein R_1 , R_2 ,
 R_3 , and R_4 are each hydrogen or alkyl.
- 5 4. The compound as in Claim 1 wherein R_3 is
hydroxy and R_1 , R_2 , and R_4 are each hydrogen or alkyl.
5. The compound as in Claim 1 wherein R_3 is alkyl
and R_1 , R_2 , and R_4 are each hydrogen.
6. The compound as in Claim 1 of the formula

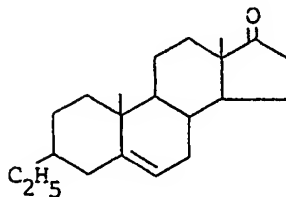
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7. The compound as in Claim 1 of the formula

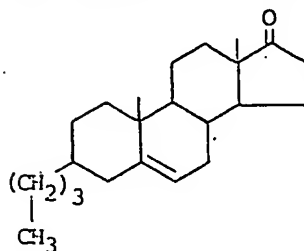
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8. The compound as in Claim 1 of the formula

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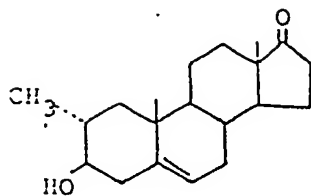


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9. The compound as in Claim 1 of the formula

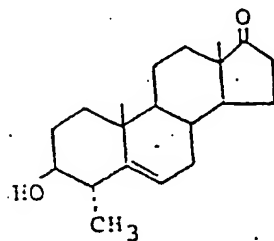
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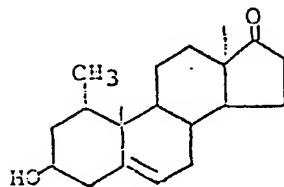
10. The compound as in Claim 1 of the formula

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11. The compound as in Claim 1 of the formula

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- 1 12. The compound as in Claim 1 which is 3- β ,
 16 α -dimethyl androst-5-en-17-one.
13. The compound as in Claim 1 which is 3- ~~β~~ -
 methyl-16 α -hydroxy-androst-5-en-17-one.
- 5 14. A therapeutic composition comprising a
 compound as in any of Claims 1-13 and a
 carrier therefor.
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